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(54) **Substituted phenyl ethanol amines, processes for their preparation and pharmaceutical compositions containing them.**

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EP 0 236 624 B1

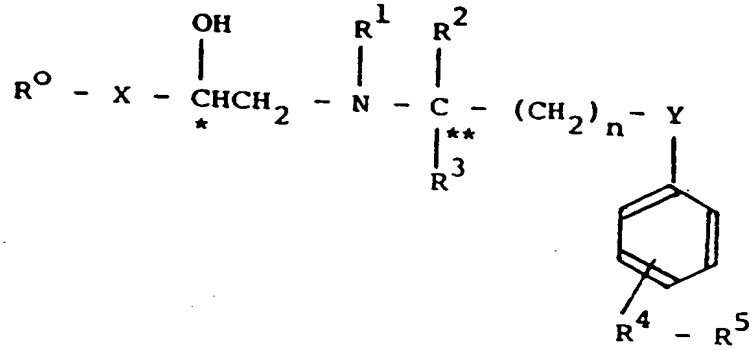
Description

The invention relates to a group of secondary or tertiary amine heterocyclic derivatives having β-agonist activity, to a process for preparing such compounds and their use in medicine and agriculture.

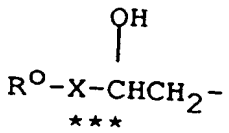
European Patent Specification, Publication Number 0,070,133 discloses certain phenoxyalkylamino-ethanolamine derivatives having inter alia anti-obesity and/or anti-hyperglycaemic activity. Some of the compounds disclosed in EP 0,070,133 are phenoxy 5-, 6- or 7-cycloalkylamino ethanolamine derivatives. EP-A-0,164,700 discloses certain bis (beta-hydroxy phenethyl) amines which disclosures represent the state of the art in accordance only with Article 54(3) EPC.

It has now been discovered that a series of novel secondary or tertiary amine heterocyclic derivatives show good β-agonist activity; they show good anti-obesity and anti-hyperglycaemic activity coupled with good selectivity from cardiac side effects.

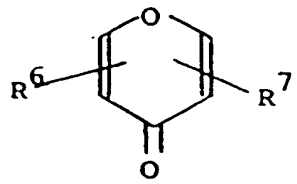
Accordingly, the invention provides a compound of the general formula (I):



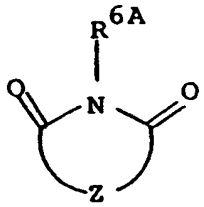
or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof,
wherein,
R^o represents a phenyl or naphthyl group optionally substituted with up to five groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy alkyl, hydroxy, amino, nitro, carboxy and pharmaceutically acceptable salts, esters and amides thereof, alkoxycarbonyl, alkoxycarbonyl alkyl alkylcarbonyloxy, or alkylcarbonyl groups or a benzofuranyl group optionally substituted in the phenyl ring with an alkyl group;
X represents a bond or $-O-CH_2-$,
R^1 represents a hydrogen atom or a moiety



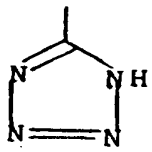
wherein R^o and X are as defined above;
R^2 and R^3 independently represent a hydrogen atom or an alkyl group,
n represents an integer 1 or 2,
Y represents a bond or a moiety $-CH_2-O-$,
R^4 represents a bond or an oxygen atom or $-R^{4A}$ or a moiety $-O-R^{4A}-$ or a moiety $-R^{4A}-O-$, wherein R^{4A} represents an alkylene group, an alkenylene group or a alkynylene group; and
R^5 represents a group of the general formula (A), (B), (C) or (D):



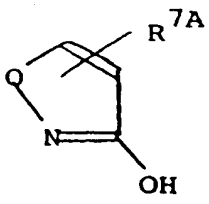
(A)



(B)

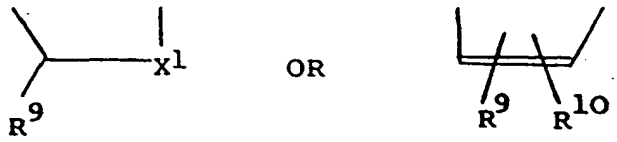


(C)



(D)

wherein R^6 and R^7 each independently represent a bond, a hydrogen atom, a hydroxyl group, an alkyloxy group; or a benzyloxy group; R^{6A} represents a bond or a hydrogen atom or an alkyl group or a carbonylalkyl group; R^{7A} represents a bond; and Z represents a moiety of formula:



wherein R^9 and R^{10} each independently represent a bond, a hydrogen atom, a hydroxyl group, an alkoxy group; and X^1 represents O, NH or S; provided that at least one of R^6 and R^7; and at least one of R^{6A}, R^9 and R^{10} represents a bond.

Preferred optional substituents for the phenyl or naphthyl group include up to three substituents selected from halogen, hydroxy, alkoxy, and hydroxy alkyl and amino.

When R^o represents a benzofuranyl group it is preferably a benzofuran-2-yl group.

When the benzofuranyl group is substituted, it is substituted in the phenyl ring with an alkyl group. Suitably, the phenyl ring in the benzofuranyl moiety is substituted in the 7-position with an alkyl group such as for example methyl or ethyl.

Preferably, when R^o represents a benzofuranyl group X represents a bond

Suitable optional substituents for R^5 include; hydroxy; alkoxy; alkyl; benzyloxy or a carbonylalkyl group.

Suitably, X represents a bond.

Favourably, R^1 represents a hydrogen atom.

Suitably, R^2 represents an alkyl group, preferably a methyl group.

Suitably, R^3 represents a hydrogen atom.

Preferably, R^{4A} represents an alkylene group, especially $-CH_2-$.

Preferably, Y represents a bond.

Preferably $-R^4-R^5$ is in the para position on the phenyl ring relative to the point of attachment of the phenyl ring to the rest of the molecule.

Preferably, n represents the integer 1.

Preferred hetero atoms in the heterocyclic group represented by R^5 are oxygen, nitrogen and sulphur

Suitably, R^5 represents the hereinbefore defined group (A).

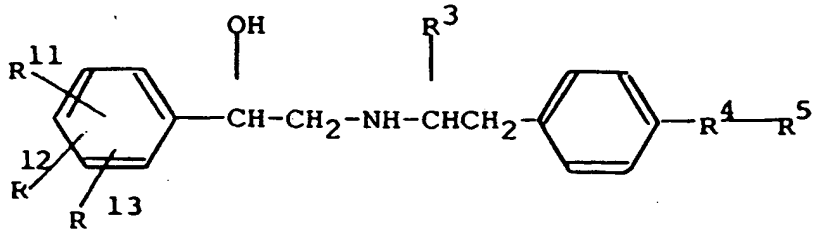
Suitably, R^5 represents the hereinbefore defined group (B).

Suitably, R^5 represents the hereinbefore defined group (C).

Suitably, R^5 represents the hereinbefore defined group (D).

Preferably, R^5 represents the hereinbefore defined group (A).

In one preferred aspect, the present invention provides a compound of formula (II):



(II)

or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, wherein R^3, R^4 and R^5 are as defined in relation to formula (I) and R^{11}, R^{12} and R^{13} each independently represent hydrogen; halogen, preferably chlorine; amino, hydroxy or hydroxymethyl.

Favourably, when R^4 represents a moiety of formula OR^{4a} wherein R^{4a} represents alkylene, R^5 represents a moiety of the hereinbefore defined formula (A) or (C).

Favourably, when R^4 represents alkylene, R^5 represents a moiety of the hereinbefore defined formula (B).

Favourably, when R^4 represents an oxygen atom, R^5 represents a moiety of the hereinbefore defined formula (D).

Favourably, when R^4 represents a bond, R^5 represents a moiety of the hereinbefore defined formula (C).

Suitably, R^{11} and R^{12} each represent a hydrogen atom.

Suitably, R^{11} and R^{12} each represent a halogen atom, preferably a chlorine atom.

Favourably, R^{11}, R^{12} and R^{13} each represent a hydrogen atom.

Favourably, R^{11} and R^{12} each represent a hydrogen atom and R^{13} represents a hydroxyl group.

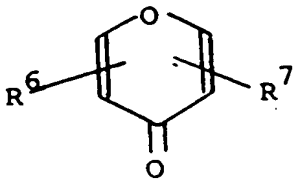
Favourably, R^{11} and R^{12} each represent a hydrogen atom, and R^{13} represents a halogen atom, preferably a chlorine atom.

Favourably, R^{11} and R^{12} each represent a chlorine atom and R^{13} represents an amino group.

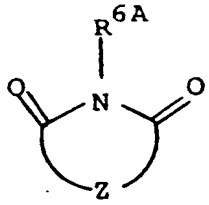
Preferably the moiety $R^{11}R^{12}R^{13}$-C_6H_3- represents a group selected from the list consisting of: phenyl, 3-chlorophenyl, 4-hydroxyphenyl and 3,5-dichloro-4-aminophenyl.

Preferably, R^3 represents a methyl group.

The moiety -R^4-R^5 represents a moiety selected from the list consisting of:



(A)



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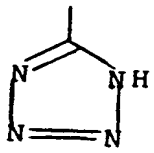
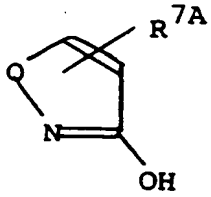
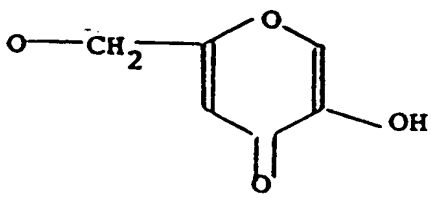


(C)



(D)

Most preferably, the moiety -R^4-R^5 represents



In a particularly-preferred aspect the present invention provides a compound selected from the group consisting of:

4-[4-[2-[(3-chloro-β-hydroxyphenethyl) amino]propyl]phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione;
4-[4-[2-[(β,4-dihydroxyphenethyl)amino]propyl]phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione;
2-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]-5-hydroxy-4H-pyran-4-one;
5-[4-[2-[(β-4-dihydroxyphenethyl)amino]propyl]benzyl] thiazolidine-2,4-dione;
5-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]benzyl]thiazolidine-2,4-dione;
5-[4-[2-[(4-amino-3,5-dichloro-β-hydroxyphenethyl) amino]propyl]benzyl]thiazolidine-2,4-dione;
5-[4-[2-[3-chloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]tetrazole;
5-[4-[2-(3-chloro-β-hydroxyphenethyl)amino]propyl] phenyl]tetrazole;
5-[4-[2-(3-chloro-β-hydroxyphenethyl)amino]propyl] phenyl]-3-hydroxyisoxazole;

or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof.

The present invention most preferably provides 4-[4-[2-[(3-chloro-β-hydroxyphenethyl) amino]propyl]-phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione;
or a pharmaceutically acceptable ester thereof;
or a pharmaceutically acceptable salt thereof.

The present invention most preferably provides 2-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]-phenoxymethyl]-5-hydroxy-4H-pyran-4-one;
or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof.

When used herein the term "alkyl", "alkenyl", "alkynyl" or "alkoxy" relates to groups having straight or branched chains containing up to 12 carbon atoms.

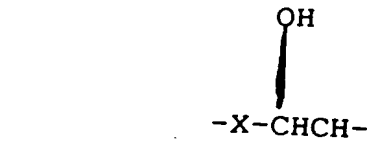
Suitable alkyl groups are C_{1-12} alkyl groups especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable alkenyl groups are C_{2-12} groups especially C_{2-6} alkenyl groups.

Suitable alkynyl groups are C_{2-12} alkynyl groups especially C_{2-6} alkynyl groups.

When used herein the term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably chlorine.

The hydroxy group present in the moiety



or any hydroxyl group present in the moiety R^6 or R^5 may be derivatised as an ester, by for example, an arylalkyl carboxylic acid or a C_{1-6}- alkyl carboxylic acid. Suitable esters are in-vivo hydrolysable esters. Such esters and pharmaceutically acceptable salts of such esters form further aspects of the present invention.

When used herein the term "in-vivo hydrolysable ester" relates to a pharmaceutically acceptable ester which readily breaks down in the human or non-human animal body to leave the free hydroxy group. Suitable in-vivo hydrolysable ester groups are those used conventionally in the art; they are preferably those provided by lower alkyl carboxylic acids.

The present invention also encompasses the salts of hydroxyl groups in for example R^5. Suitable such salts are metal salts especially alkali metal salts for example sodium salts.

Preferably the above mentioned hydroxyl groups are present as free hydroxyl groups.

The compounds of the general formula (I) may have, depending on the meaning of R^1, R^2, R^3 and R^5, up to four asymmetric carbon atoms, marked with asterisks in the formula. These compounds may, therefore, exist in up to sixteen stereoisomeric forms. The present invention encompasses all stereoisomers of the compounds of the general formula (I) whether free from other isomers or admixed with other isomers in any proportion, and thus includes for instance, racemic mixtures of enantiomers.

The absolute configuration of any compound of the general formula (I) may be determined by conventional X-ray crystallographic techniques.

Suitably, when R^2 = R^3, the '*' asymmetric carbon has the R-configuration.

Suitably, when X represents a bond, the '*' asymmetric carbon has the R configuration.

Suitably, when X represents -0-CH_2, the '*' asymmetric carbon has the S-configuration.

Suitably, when X represents a bond, the '**' asymmetric carbon has the R-configuration.

Suitably, when X represents -0-CH_2 the '*' asymmetric carbon has the S-configuration.

When R^1 = H and R^2 = R^3, a preferred enantiomer of the compounds of formula (I) is that wherein the asymmetric carbons have the following configurations:

'*' = R; and '*' = R; or

'*' = S; and '*' = R.

When R^1 = H and R^2 = R^3, a preferred enantiomer of the compound of formula (I) is that wherein the asymmetric carbons have the following configurations:

'*' = R; '*' = R; '*' = R; or

'*' = S; '*' = R; '*' = R; or

'*' = R; '*' = R; '*' = S; or

'*' = S; '*' = R; '*' = S.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethyl- amine, dehydroabietylamine, N,N'-bisdehydro- abietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

Compounds of the general formula (I) also form acid addition salts.

Pharmaceutically acceptable acid addition salts may be, for example, salts with inorganic acids such, for example, as hydrochloric acid, hydrobromic acid, orthophosphoric acid or sulphuric acid, or with organic acids such; for example as methanesulphonic acid, toluenesulphonic acid, acetic acid, propionic acid, lactic acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid or acetylsalicylic acid.

Pharmaceutically acceptable amides include amides of formula -$CONR^sR^t$ wherein R^s and R^t each independently represents hydrogen or C_{1-6} alkyl, or R^s and R^t together with the nitrogen atom to which they are attached form a saturated 5- or 6- membered ring.

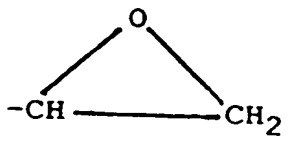
Solvates, preferably hydrates, of the compound of formula (I) are also encompassed by the invention.

The invention also provides a process for the preparation of a compound of the general formula (I) or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, which comprises either:

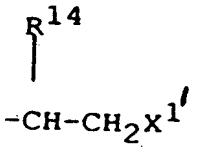
(A) reacting a compound of the general formula (III)

R^o-X-Q (III)

wherein R^o and X are as defined in relation to formula (I) and Q represents a group of formula (a) or (b):



(a)

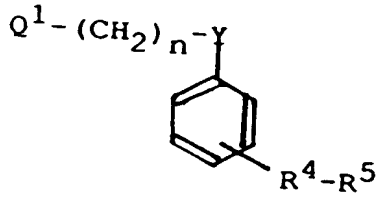


(b)

wherein

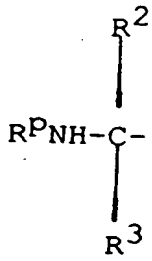
R^{14} represents a hydroxyl group or a protected hydroxyl group, and $X^{1'}$ represents a leaving group,

with a compound of the general formula (IV):



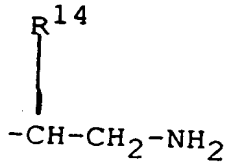
(IV)

wherein R^4, R^5, n and Y are as defined in relation to formula (I), and
Q^1 represents a group of the formula (F):



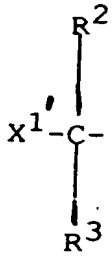
(F)

wherein R^2 and R^3 are as defined in relation to formula (I), and R^P represents a hydrogen atom, a protecting group, preferably a benzyl group, or the hereinbefore defined moiety R^1;
or in the abovementioned compound of formula (III) Q represents a group of the formula (c):



(c)

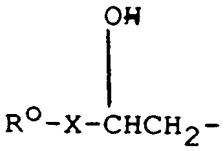
wherein R^{14} has the meaning given above, and in the abovementioned compound of formula (IV) Q^1 represents a group of the formula (g):



(g)

in which R^2, R^3 and $X^{1'}$ have the meanings given above; or

(B) for compounds of formula (I) wherein R^1 represents only the moiety



as defined above, by reacting a compound of formula (I) wherein R^1 represents a hydrogen atom, with either:

(i) a compound of formula (IIIA):

R^o-X-Q (IIIA)

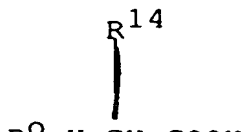
wherein R^o and X are as defined in relation to formula (I) and Q represents a group of the hereinbefore defined formula (a) or (b); or

(ii) a compound of formula (V):

R^o-X-CO-CHO (V)

wherein R^o and X are as defined in relation to formula (I); and subsequently treating with a reducing agent; or

(iii) a compound of formula (VI):



(VI)

wherein R^o and X are as defined in relation to formula (I) and R^{14} represents a hydroxyl group or a protected hydroxyl group; and subsequently reducing the resulting hydroxyamide; and thereafter if necessary carrying out one or more of the following steps;

i) removing any protecting group;

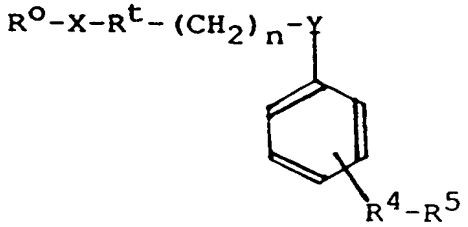
ii) converting a compound of formula (I) into a further compound of formula (I);

iii) converting a salt of formula (I) into a free compound of formula (I);

iv) preparing a pharmaceutically acceptable ester of a compound of formula (I);

v) preparing a pharmaceutically acceptable salt of a compound of formula (I) or an ester thereof.

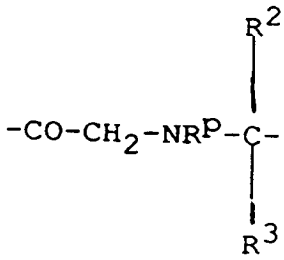
The present invention also provides a process for the preparation of a compound of the general formula (I) or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, which comprises reducing a compound of the general formula (VII):



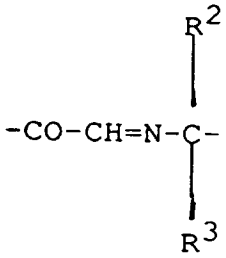
(VII)

in which

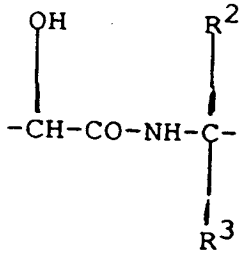
R^o, R^4, R^5, X, Y and n are as defined in relation to formula (I), and R^t represents a group of formula:



(i),

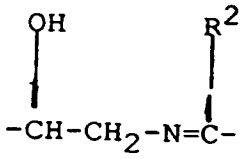


(ii),



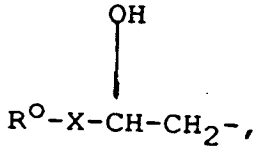
(iii),

or



(iv)

in which R^P is hydrogen or a protecting group, preferably a benzyl group, R^2 and R^3 are as defined in relation to formula (I);
and if required converting a compound of formula (I) wherein R^1 represents hydrogen into a compound of formula (I) wherein R^1 represents a moiety of formula



wherein R^o and X are as defined above, by reacting the compound of formula (I) wherein R^1 represents hydrogen with a compound of formula (IIIA), (V) or (VI) as described hereinbefore; and thereafter if

necessary carrying out one or more of the following steps;

i) removing any protecting group;

ii) converting a compound of formula (I) into a further compound of formula (I);

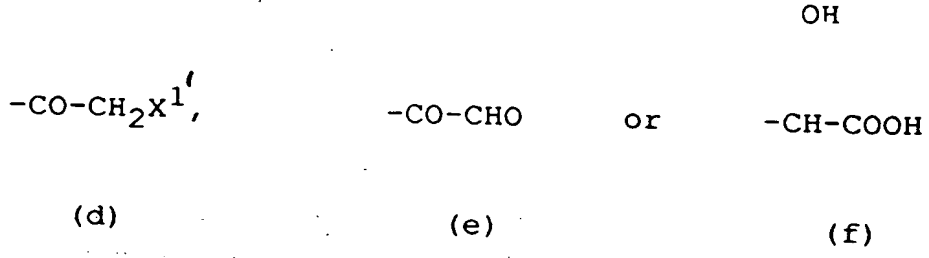
iii) converting a salt of formula (I) into a free compound of formula (I);

iv) preparing a pharmaceutically acceptable ester of a compound of formula (I);

v) preparing a pharmaceutically acceptable salt of a compound of formula (I) or an ester thereof.

The starting materials of the general formula (VII) may be prepared, for example, by reacting compounds of the general formulae (III) and (IV) in which:

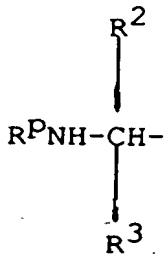
R^o and X are as defined in relation to formula (III) and Q represents a group of the formula (d), (e) or (f):



(d) (e) (f)

wherein $X^{1'}$ is as defined in relation to formula (III), and

Q^1 represents a group of the formula (F^1)

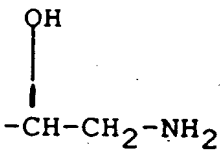


(F^1)

wherein R^2 and R^3 are as defined in relation to formula (I) and R^P is a hydrogen atom or a benzyl group;

or, in the case of compounds of formula (VII) wherein R^3 represents hydrogen,

Q represents a group of the formula (c):



(c)

and Q^1 represents a group of the formula (J):

(J)

in which R^2 has the meaning given above.

Any protecting groups used in the above reactions are those used conventionally in the art. For example when R^o represents a phenyl group substituted with a hydroxy group, any conventional hydroxy protecting group may be used. Preferably the hydroxy group being protected by etherification; the ether group being converted into a free hydroxy group by methods known per se. For example, an unsubstituted or substituted benzyloxy protecting group, may be converted by hydrogenolysis into a free hydroxy group. The hydrogenolysis reaction may be carried out, for example in the presence of a palladium-on-carbon catalyst in a solvent, for example a mixture of ethyl acetate and methanol.

A leaving group $X^{1'}$ is any group that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable examples of such groups are halogen atoms, mesyloxy groups and tosyloxy groups. Preferably in formula (b) of compound (III) or in formula (g) of compound (IV) $X^{1'}$ represents a mesyloxy or tosyloxy group or a bromine atom, and in formula (d) of compound (III) $X^{1'}$ represents a bromine atom.

Compounds of formulae (III), (IIIA) and (IV) are either known compounds or can be prepared from known compounds by known processes or processes analogous to known processes.

The reaction of compounds of the general formulae (III) and (IV) in which Q and Q^1 have formulae (a) and (F) respectively is advantageously carried out in a protic solvent, e.g. an alkanol, especially a lower alkanol having at least 2 carbon atoms, at reflux, preferably in ethanol.

The reaction between the compounds of formula (I) (wherein R^1 = H) and (IIIA) (wherein Q = (a)) may be carried out under similar conditions.

Reaction of compounds of the general formulae (III) and (IV) in which Q and Q^1 have formulae (b) and (F) or (c) and (G) respectively is advantageously carried out in dimethyl sulphoxide, for example at a temperature in the range of from 30 to 80 °C, e.g. substantially 50 °C, and advantageously for a period of time of 1 to 4 days, e.g. about 3 days. The reaction between the compounds of formula (I) (wherein R^1 = H) and (IIIA) (wherein Q = (b)) may be carried out under similar conditions.

The reaction of the compounds of the general formulae (III) and (IV) in which Q and Q^1 have formulae (d) and (F) respectively is advantageously carried out in butanone or acetonitrile at reflux, if desired in the presence of a base.

The reaction of compounds of the general formula (III) and (IV) in which Q and Q^1 have formulae (e) and (F) or (c) and (J) respectively is preferably carried out in benzene using a Dean and Stark apparatus, more especially at reflux.

The reaction of compounds of the general formulae (III) and (IV) in which Q and Q^1 have formulae (f) and (F) respectively is preferably carried out in the presence of dicyclohexyl carbodiimide or other suitable condensing agent.

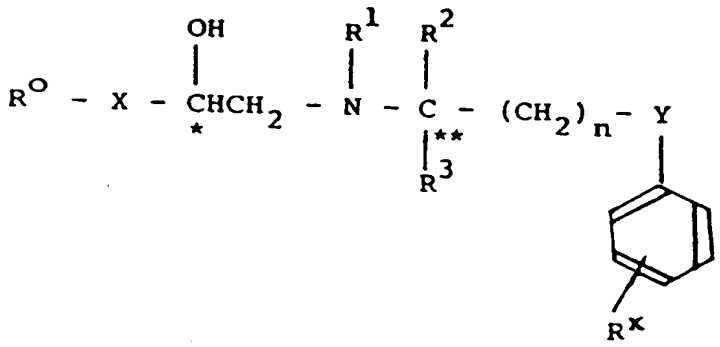
The reduction of a compound of the general formula (VII) may be carried out, for example, when R^1 represents a group of the formula (i) and (ii) with sodium borohydride; when R^1 represents a group of the formula (iii) with a borane reducing agent, for example borane methyl sulphide complex, and when R^1 represents a group of the formula (iv) with sodium borohydride or sodium cyanoborohydride, or catalytically, for example by hydrogen in the presence of platinum or palladium.

The reaction between the compounds of formula (I) (wherein R^1 = H) and (V) is preferably carried out in methanol at ambient temperature, the subsequent reduction being carried out, for example, with sodium cyanoborohydride.

The reaction between the compounds of formula (I) (wherein R^1 = H) and (VI) is preferably caried out in the presence of dicyclohexyl carbodimide or other suitable condensing agent; the subsequent reduction may be carried out with, for example, lithium aluminium hydride or a borane reducing agent, for example borane methyl sulphide complex.

The reductions with sodium cyanoborohydride and sodium borohydride are preferably performed in a lower alkanol, e.g. methanol.

In a further aspect the present invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, from a compound of formula (VIII):



(VIII)

wherein R^0, R^1, R^2, R^3, X, n and Y are as defined in relation to formula (I) and R^x is a moiety convertible to a moiety $-R^4-R^5$; and thereafter if necessary carrying out one or more of the following steps;

i) removing any protecting group;

ii) converting a compound of formula (I) into a further compound of formula (I);

iii) converting a salt of formula (I) into a free compound of formula (I);

iv) preparing a pharmaceutically acceptable ester of a compound of formula (I);

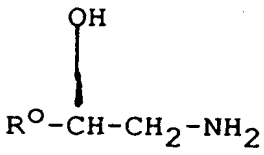
v) preparing a pharmaceutically acceptable salt of a compound of formula (I) or an ester thereof.

Suitable moieties R^x are those which are convertible to moieties $-R^4-R^5$ by conventional methods, for example:

R^x may represent a moiety R^4-CN, wherein R^4 is as defined in relation to formula (I), which may be treatment with an azide, such as ammonium azide, thereby converting the moiety R^4-CN to a moiety $-R^4-R^5$ wherein R^5 is tetrazolyl.

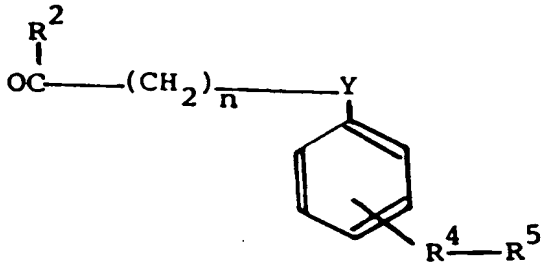
Compounds of the hereinbefore defined compound of formula (VIII) may be prepared where appropriate by analogous methods to those used for the compounds of formula (I).

In a preferred method of preparing a compound of the general formula (I) wherein R^1 represents hydrogen, or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, a compound of formula (IIIc):



(IIIc)

wherein R^o is as defined in relation to formula (I), is reacted with a compound of the general formula (IVJ):



(IVJ)

wherein R^2, R^4, R^5, Y, and n are as defined in relation to formula (I), to provide a compound of the general formula (VII) wherein R^1 represents a group of the general formula (iv): the said compound of formula (V) is then reduced with sodium cyanoborohydride, preferably in methanol; and thereafter if necessary carrying out one or more of the following steps;

i) removing any protecting group;

ii) converting a compound of formula (I) into a further compound of formula (I);

iii) converting a salt of formula (I) into a free compound of formula (I);

iv) preparing a pharmaceutically acceptable ester of a compound of formula (I);

v) preparing a pharmaceutically acceptable salt of a compound of formula (I) or an ester thereof.

The salts of compounds of the general formula (I) may be produced by methods conventional in the art, for example, acid addition salts may be prepared by treating a compound of general formula (I) or pharmaceutically acceptable esters thereof with the appropriate acid.

Compounds of the general formula (I) or pharmaceutically acceptable esters thereof and salts thereof, produced by the above processes, may be recovered by conventional methods.

Compounds of the general formula (I) may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallisation from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.
Suitable optically active acids which maybe used as resolving agents are described in 'Topics in Stereochemistry', Vol. 6, Wiley Interscience, 1971, Allinger, N.L. and Eliel, W.L. Eds.

Alternatively, any enantiomer of a compound of the general formula (I) may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

As previously indicated, the compounds of the present invention have valuable pharmacological properties.

The present invention also provides a compound of the general formula (I) or a pharmaceutically acceptable ester; or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

In one aspect, the present invention provides a compound of the general formula (I) or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof for use in the treatment of obesity in human or non-human animals.

Suitable non-human animals are non-human mammals.

The present invention further provides a compound of the general formula (I), or a pharmaceutically acceptable ester thereof; or pharmaceutically acceptable salt thereof, for use in the treatment of hyperglycaemia in human or non-human animals.

A compound of the general formula (I) or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I) or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier therefor.

As used herein the term "pharmaceutically acceptable" embraces compounds, compositions and ingredients for both human and veterinary use: for example the term "pharmaceutically acceptable salt" embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection, are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

In treating hyperglycaemic or obese humans the compound of the general formula (I) or pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In treating hyperglycaemic or obese non-human animals, especially dogs, the active ingredient may be adminstered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg.

The present invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of obesity or hyperglycaemia.

In a further aspect the present invention also provides a method for increasing weight gain and/or improving the feed utilisation efficiency and/or increasing lean body mass and/or decreasing birth mortality rate and increasing the post-natal survival rate; of livestock, which method comprises the administration to livestock of an effective non-toxic amount of a compound of formula (I) or a veterinarily acceptable ester thereof; or a veterinarily acceptable salt thereof.

A suitable method is for increasing weight gain and/or improving the feed utilisation efficiency and/or increasing the lean body mass of livestock.

Whilst the compounds of formula (I) and the veterinarily acceptable esters thereof; or veterinarily acceptable salts thereof may be administered to any livestock in the abovementioned method, they are particularly suitable for increasing the weight gain and/or feed utilisation efficiency and/or lean body mass and/or decreasing birth mortality rate and increasing the post-natal survival rate; in poultry, especially turkeys and chickens, cattle, pigs and sheep.

In the preceding method the compounds of formula (I) or veterinarily acceptable esters thereof; or veterinarily acceptable salts thereof will normally be administered orally although non-oral modes of administration, for example injection or implantation, are also envisaged. Suitably the compounds are administered in the feed-stuff or drinking water provided for the livestock. Conveniently these are administered in the feed-stuff at from 10^{-3} ppm - 500ppm of total daily fed intake, more usually 0.01ppm to 250ppm, suitably less than 100ppm.

The particular formulations used will of course depend upon the mode of administration but will be those used conventionally in the mode of administration chosen.

For administration in feed-stuff the drugs are conveniently formulated as a premix in association with a suitable carrier.

Accordingly, the present invention also provides a veterinarily acceptable premix formulation comprising a compound of formula (I) or a veterinarily acceptable ester thereof; or a veterinarily acceptable salt thereof in association with a veterinarily acceptable carrier therefore.

Suitable carriers are inert conventional agents such as powdered starch. Other conventional feed-stuff premix carriers may also be employed.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt thereof is administered in any of the abovementioned dosage ranges.

The following Examples illustrate the invention but do not limit it in any way.

Example 1

4-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl] phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione, hemihydrate

A solution of 2-(3-chlorophenyl)-2-hydroxy ethylamine (0.6g) and the sodium salt of 4-[4-acetonylphenoxy]-3-hydroxy-1H-pyrrole-2,5-dione(1.0g) in ethanol, was treated with sodium cyanoborohydride (0.25g) and stirred at ambient temperature for 18h. The solvent was evaporated in vacuo, the residue shaken with ethyl acetate and water and filtered. The insoluble material was washed with acetone and crystallised from methanol: water (95:5) to give 4-[4-[2-[(3-chloro-β-hydroxy-phenethyl)amino]-propyl]phenoxy]-3-hydroxy-1H- pyrrole-2,5-dione, hemihydrate, (0.55g), as a (27:73)mixture of diastereoisomers.

'H NMR (DMSO-d_6)ppm:

1.0 (3H,dd);2.4(1H,m);3.0 - 3.3(4H,m);5.0(1H,m), 6.8(2H,d);7.0(2H,d);7.4(4H,m);8.0-9.5(1H, very broad exch.D_2O);9.1(2H, broad s,exch.D_2O).

Example 2

4-[4-[2-[(β,4-Dihydroxyphenethyl)amino]propyl]phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione,hydrate

A solution of 2-(4-benzyloxyphenyl)-2-hydroxy-ethylamine (0.48g) and 4-[4-acetonylphenoxy]-3-hydroxy-1H-pyrrole-2,5-dione, sodium salt (0.56g) in methanol was treated with sodium cyanoborohydride (0.15g) and stirred at ambient temperature for 18 h. The solvent was evaporated in vacuo, the residue shaken with ethyl acetate and water and filtered. The residue was washed with acetone, dissolved in glacial acetic acid and hydrogenated at ambient temperature and pressure over 10% palladium on charcoal. After filtration and evaporation of the solvent in vacuo the residue was crystallised from acetonitrile:water (95:5) to give 4-[4-[2-[(β,4-dihydroxyphenethyl)amino]propyl]phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione,hydrate, (0.2g), as a (10:90) mixture of diastereoisomers.

'H NMR (DMSO-d_6)ppm:

1.0 (3H,d); 2.5(1H,m);3.0(3H,m);3.25(1H,m);3.25- 3.5(3H, broad exch.D_2O); 4.75(1H,m); 5.25-6.3(1H, very broad, exch.D_2O); 6.75(4H,dd); 7.1(2H,d); 7.2(2H,d);7.5 - 8.75(1H, very broad exch D_2O); 8.9(1H,s exch.D_2O); 9.4(1H, broad exch.D_2O).

Example 3

2-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]-5-hydroxy-4H-pyran-4-one.

A solution of 2-(4-acetonylphenoxymethyl)-5-hydroxy-4H-pyran-4-one (0.7g) and 2-(3-chlorophenyl)-2-hydroxyethylamine carbonate 0.52g in benzene was heated under reflux for 2.5h using a Dean and Stark head. The reaction mixture was allowed to cool and the solvent removed in vacuo. The residue was taken up in methanol, treated with sodium cyanoborohydride (0.2g) and stirred at ambient temperature for 18 h. The solvent was evaporated under reduced pressure, the residue dissolved in ethyl acetate, washed with water (2x50ml), brine(1x50ml) and dried (magnesium sulphate). After filtration and evaporation of solvent the residue was purified by column chromatography on silica using methanol:chloroform (3:97) as eluent, followed by crystallisation from acetone to give 2-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]-phenoxymethyl]- 5-hydroxy-4H-pyran-4-one, (0.1g), as a (35:65) mixture of diastereoisomers.

'H NMR(DMSO-d_6)ppm:

0.9(3H,d);2.3-2.8(5H,m); 3.0-4.2(1H, very broad, exch.D_2O); 4.6(1H,m); 4.75-6.25(2H, very broad, exch.D_2O); 4.9(2H,s); 6.5(1H,s); 6.8(2H,m); 7.1(2H,m); 7.3(4H,m) 8.1(1H,s).

Example 4

5-[4-[2-[(β-4-Dihydroxyphenethyl)amino]propyl]benzyl] thiazolidine-2,4-dione.

A mixture of the sodium salt of octopamine (0.35g) and 5-(4-acetonylbenzyl)thiazolidine-2,4-dione (0.52g) in methanol was treated with sodium cyanoborohydride (0.15g) and stirred for 18h at ambient temperature. The solvent was removed in vacuo and the residue purified by column chromotography using acetone as eluent to give 5-[4-[2-[(β-4-dihydroxyphenethyl) amino]propyl]benzyl] thiazolidine-2,4-dione, (0.3g), as a (45:55) mixture of diastereoisomers.

'H NMR ($DMSOd_6$) ppm:

1.0(3H,d); 2.5(1H,m); 2.8(4H,m); 3.2(1H,m); 3.3(1H,m);4.5(1H,m); 4.7(1H,m); 5.0-7.5(4H, very broad, exch.D_2O); 6.4(2H,d); 7.2(6H,m).

Example 5

5-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl]benzyl]thiazolidine-2,4-dione,hemihydrate.

A mixture of 5-(4-acetonylbenzyl)thiazolidine-2,4-dione (0.9g) and 2-(3-chlorophenyl)-2-hydroxyethylamine (0.6g) in dry benzene (80ml) was heated under reflux, with azeotropic removal of water, for 1h. The solvent was evaporated, and the residue dissolved in methanol (80ml) and treated with sodium cyanoborohydride (0.5g). After 16h at ambient temperature the methanol was evaporated and the residue partitioned between ethyl acetate and water. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to a foam which was chromatographed on silica gel. Elution with methanol in chloroform (6:94) gave 5-[4-[2-[(3-chloro-β- hydroxyphenethyl)amino]propyl]benzyl]thiazolidine-2, 4-dione,hemihydrate as a white crystalline solid (ethyl acetate), mp. 149-160 °C as a 54:46 mixture of diastereoisomers.

'H NMR (DMSO-d_6)ppm:

0.97(3H,d); 2.72-3.08(5H,m); 3.15-3.90 (2H,m + 4H, broad exch. D_2O); 4.68(2H,m); 7.13(4H,m); 7.27-7.53-(4H,m).

Example 6

5-[4-[2-[(4-Amino-3,5-dichloro-β-hydroxyphenethyl) amino]propyl]benzyl]thiazolidine-2,4-dione.

5-[4-[2-[(4-Amino-3,5-dichloro-β-hydroxyphenethyl) amino]propyl]benzyl]thiazolidine-2,4-dione was prepared as a 46:54 mixture of diastereoisomers, mp. 195-201 °C, from 2-(4-amino-3,5-dichlorophenyl)-2-hydroxy ethylamine and 5-(4-acetonylbenzyl)thiazolidine- 2,4-dione in an analogous manner to that described in Example 5

'H NMR (DMSO-d_6)ppm:

0.95(3H,d); 2.68-3.08(5H,m); 3.20-4.30(2H,m + 3H, broad, exch.D_2O); 4.56(2H,m); 5.38(2H,s, exch.D_2O); 7.13(4H,m); 7.21(2H,s).

Example 7

5-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]tetrazole.

A mixture of 4-[2-[(3-chloro-β-hydroxyphenethyl)amino]phenoxyacetonitrile (0.5g), sodium azide (96mg), and ammonium chloride (80mg) in dry dimethylformamide was heated at 100 °C for 6h. The reaction was cooled and the solvent evaporated in vacuo. The residue was chromatographed on silica using methanol-chloroform (5:95) as eluent until starting materials had eluted; the solvent was then changed to methanol-chloroform (20:80) to give 5-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]-tetrazole, (0.45g) as a (46:54) mixture of diastereoisomers.

^{1}H NMR (DMSO-d_6) ppm:

1.1(3H,d); 2.6(1H,m); 3.0-3.4(4H,m); 4.5-6.5(3H, very broad exch.D_2O); 4.9(1H,m); 5.2(2H,s); 6.9(2H,d); 7.15-(2H,m); 7.4(4H,m)

Example 8

5-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl]phenyl]tetrazole.

A mixture of 2-(3-chlorophenyl)-2-hydroxyethylamine carbonate (1.1g) and 5-(4-acetonylphenyl)tetrazole in benzene was heated under reflux for 3h using a Dean and Stark head. The reaction mixture was cooled and the solvent evaporated in vacuo. The residue was dissolved in methanol, and treated with sodium cyanoborohydride (0.5g) and stirred at ambient temperature for 24h. The solvent was evaporated in vacuo, the residue treated with water, evaporated to dryness, and purified by column chromatography on silica using methanol- chloroform (15:85) as eluent to give 5-[4-[2-(3-chloro-β-hydroxyphenethyl)amino]propyl]-phenyl]tet razole, (0.57g), as a 51:49 mixture of diastereoisomers.

^{1}H NMR(DMSO-d_6) ppm:

1.1(3H,d); 2.4-2.9(1H,m); 2.9-3.7(4H,m); 5.0(1H,m); 7.0(3H broad s,exch.D_2O); 7.35(6H,m); 8.0(2H,d).

Example 9

5-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl]phenyl]-3-hydroxyisoxazole.

A solution of 2-(3-chlorophenyl)-2-hydroxyethylamine (0.5g) and 5-(4-acetonylphenyl)-3-hydroxyisoxazole (0.5g) in benzene was heated under reflux for 3h, using a Dean and Stark head, cooled and the solvent evaporated in vacuo. The residue was dissolved in methanol, treated with sodium cyanoborohydride (0.175g) at ambient temperature for 16h and the solvent removed in vacuo. The residue was treated with water, filtered, washed with a little acetone and recrystallised from acetonitrile to give 5-[4-[2-(3-chloro-β-hydroxyphenethyl) amino]propyl]phenyl]-3-hydroxyisoxazole, (0.12g), as a (62:38) mixture of diastereoisomers.

^{1}H NMR(DMSO-d_6) ppm:

1.0(3H,d); 2.6-3.0(5H,m); 4.7(1H,m); 4.75-6.25(3H, very broad exch.D_2O); 6.4(1H,s); 7.3(6H,m); 7.7(2H,m).

Example 10

2-[4-[2-[(β,4-Dihydroxyphenethyl)amino]propyl]phenoxymethyl]-5-hydroxy-4H-pyran-4-one

A mixture of the sodium salt of octopamine (0.65g), and 2-(4-acetonylphenoxymethyl)-5-hydroxy-4H-pyran-4-one (1.0g) in methanol was treated with sodium cyanoborohydride (0.3g) and stirred at ambient temperature for 18 hours. The solvent was evaporated in vacuo. The residue was suspended in acetone and filtered, washed with acetone and then purified by column chromatography on silica using 5% methanol : chloroform as eluent-increasing to 15% methanol : chloroform after elution of fast-running impurities. This gave 2-[4-[2-[(β,4-dihydroxyphenethyl)amino]propyl]phenoxymethyl]-5-hydroxy-4H-pyran-4-one(0.4g) as a (50:50) mixture of diastereoisomers.

^{1}H NMR (DMSO-d_6) ppm:

0.9 (3H,d); 2.3-3.0 (5H,m); 4.5 (1H,m); 4.9 (2H,s); 6.5 (1H,s); 6.6-7.3 (8H,m); 8.1 (1H,s); 8.3-3.5 (4H, very broad, exchanged with D_2O).

Example 11

2-[4-[2-[(4-Amino-3,5-dichloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]-5-hydroxy-4H-pyran-4-one

A solution of 2-[4-acetonylphenoxymethyl]-5-hydroxy -4H-pyran-4-one (1.0g) and 2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethylamine (0.75g) in benzene, was heated to reflux for 3 hours under a Dean and Stark head. After cooling, the solvent was removed in vacuo, the residue dissolved in methanol, treated with sodium cyanoborohydride (0.25g) and then stirred at ambient temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in ethyl acetate and washed with water (2x50ml), brine (1x50ml) and dried ($MgSO_4$). After filtration and evaporation of solvent the residue was purified by column chromatography on silica using 3% methanol : chloroform as eluent to give 2-[4-[2-[(4-amino-3,5-dichloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl] -5-hydroxy-4H-pyran-4-one as a (40:60) mixture of diastereoisomers.

^{1}H NMR (DMSO-d_6) ppm:

0.9 (3H,d); 2.3-2.8 (5H,m); 4.4 (1H,m); 4.9 (2H,s); 5.3 (2H,s, exchanged with D_2O); 5.8-4.6 (3H, very broad, exchanged with D_2O); 6.5 (1H,s) 6.8-7.2 (6H,m); 8.1 (1H,s).

Example 12

4-[4-[2-[(4-Amino-3,5-dichloro-β-hydroxyphenethyl) amino]propyl]phenoxy-3-hydroxy-1H-pyrrole-2,5-dione, hemihydrate

A solution of the sodium salt of 4-(4-acetonylphenoxy)-3-hydroxy-1H-pyrrole-2,5-dione (1.41g) and 2-(4-amino-3,5-dichlorophenyl)-2-hydroxy ethylamine (1.0g) in methanol was treated with sodium cyanoborohydride (0.35g) and stirred at ambient temperature for 18 hours. The solvent was removed in vacuo, the residue dissolved in acetone and purified by column chromatography on silica using acetone as eluent followed by methanol after the elution of fast-running impurities. The solid obtained was washed with acetone and filtered to give 4-[4-[2-[(4-amino-3,5-dichloro-β-hydroxyphenethyl)amino]propyl]phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione hemihydrate as a (34:66) mixture of diastereoisomers.

1H NMR (DMSO-d_6) ppm:

0.9 (3H,m); 2.9-3.5 (5H,m); 4.8 (1H,m); 5.5 (2H,s, exchanged with D_2O); 6.5-5.2 (1H, broad, exchanged with D_2O); 6.8 (2H,d); 7.0 (2H,d); 7.3 (2H,s); 9.1 (1H,s, exchanged with D_2O); 9.5-8 (2H, very broad, exchanged with D_2O).

Example 13

5-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl] phenoxymethyl]3-hydroxyisoxazole.

A solution of 5-(4-acetonylphenoxymethyl)-3-hydroxyisoxazole (0.6g) and 3-chloro-β-hydroxy phenethylamine (0.42g) in benzene, was heated under reflux for 3h using a Dean and Stark head.

The reaction was cooled and the solvent removed in vacuo. The residue was dissolved in methanol, treated with sodium cyanoborohydride (0.2g) and stirred at room temperature for 18h. The solvent was removed in vacuo, the residue triturated with ethyl acetate, filtered and chromatographed on silica. Elution with chloroform: methanol (95:5) gave 5-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]-3-hydroxyisoxazole (0.3g) as a 55:45 mixture of diastereoisomers.

^{1}H NMR (DMSO-d_6) ppm:

0.9 (3H,d); 2.3-2.9 (5H,m); 3.0-4.0 (2H, broad, exchanges with D_2O); 4.6 (1H,m); 4.8(2H,s); 5.0-6.4 (1H, very broad, exchanges with D_2O); 5.4 (1H,s); 6.8 (2H,m); 7.1 (2H,m); 7.2-7.5 (4H,m).

Example 14

2-[4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl] phenoxymethyl]-5-hydroxy-6-dimethylaminomethyl-4H-pyran-4-one.

A solution of 2-[4-[2-[(3-chloro-β-hydroxyphenethyl) amino]propyl]phenoxymethyl]-5-hydroxy-4H-pyran-4-one (0.8g) in ethanol, was added to a mixture of dimethylamine (0.28ml of a 33% solution, in ethanol) and formaldehyde (0.175ml of a 37% aq. solution) in ethanol: water (95:5), (50ml), at room temperature and allowed to stand for 1h. The solvent was evaporated in vacuo, the residue was partitioned between ethyl acetate and water separated and the organic extracts dried (magnesium sulphate), filtered and evaporated to an oil which was chromatographed on silica. Elution with chloroform: methanol (95:5) gave 2-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl] phenoxymethyl]-5-hydroxy-6-dimethylaminomethyl-4H-pyran-4-one (0.4g) as a 49:51 mixture of diastereoisomers.

^{1}H NMR (DMSO-d_6) ppm:

0.9 (3H,d); 2.2 (6H,s); 2.25 (5H,m); 3.5 (2H,s); 3.8-6.2 (3H, very broad, exchanges with D_2O); 4.6 (1H,m); 5.0(2H,s); 6.5 (1H,s); 6.9 (2H,m); 7.1 (2H, m); 7.2-7.5 (4H,m).

Preparation of Intermediate Products

Example X1

4-[4-Acetonylphenoxy]-3-hydroxy-1H-pyrrole-2,5-dione.

A solution of 4-acetonylphenoxyacetamide, ethylene ketal (3.2g) and diethyl oxalate (2.01g) in dry dimethylformamide at 0°C was treated with potassium tert-butoxide (3.24g) in two portions at 15 min. intervals. The solution was then stirred 16h at ambient temperature, poured into water, and acidified with 6N hydrochloric acid. The aqueous solution was extracted with ethyl acetate, the combined organic extracts dried (magnesium sulphate), filtered and evaporated and the residue crystallised from acetone/ether to give 4-[4-acetonylphenoxy]-3-hydroxy- 1H-pyrrole-2,5-dione, (1.5g).

^{1}H NMR ($CDCl_3$ and DMSO-d_6):

2.2(3H,S); 3.6(2H,s); 7.0(4H,m);9.8(1H,s + 1H very broad).

This material was converted to the sodium salt by treatment with an equivalent of sodium hydroxide in aqueous solution, evaporating to dryness and azeotroping residual water with benzene. The sodium salt was used without further purification.

Example X2

2-(4-Acetonylphenoxymethyl)-5-benzyloxy-4H-pyran- 4-one, ethylene ketal

A mixture of 4-hydroxyphenylpropan-2-one, ethylene ketal (3.88g), 5-benzyloxy-2-chloromethyl-4H-pyran-4- one (5.0g) and potassium carbonate (3.5g) in acetone, was heated under reflux for 18h. The reaction mixture was cooled, filtered and the solvent removed in vacuo. The residue was dissolved in ethyl acetate, washed with 2N-sodium hydroxide solution (1x50ml), water (2x50ml), dried (magnesium sulphate), filtered and evaporated to dryness in vacuo. The residue was purified by column chromatography on silica using chloroform as eluent, followed by crystallisation from acetone to give 2-(4-acetonylphenoxymethyl)-5-benzyloxy-4H-pyran-4-one ethylene ketal, (5.3g).

^{1}H NMR ($CDCl_3$) ppm:

1.3(3H,s);2.8(2H,s);3.8(4H,m);4.8(2H,s);5.1(2H,s); 6.55(1H,s);6.8(2H,d);7.2(2H,d);7.35(5H,s);7.6(1H,s).

Example X3

2-(4-Acetonylphenoxymethyl)-5-hydroxy-4H-pyran-4-one

A solution of 2-(4-acetonylphenoxymethyl)-5-benzyloxy-4H-pyran-4-one, ethylene ketal (2.0g) in methanol was hydrogenated at ambient temperature and pressure over 10% palladium on carbon until absorption of hydrogen was complete. The catalyst was filtered off and the solvent removed in vacuo. The residue was dissolved in acetone (75ml) and treated with 2N-hydrochloric acid solution (2ml) and allowed to stand at room temperature for 2h. The solvent was then removed in vacuo, the residue dissolved in ethyl acetate, washed with water (2x50ml), brine (1x50ml) and dried (magnesium sulphate). After filtration and evaporation of the solvent, the residue was purified by column chromatography on silica using methanol-chloroform (2:98) as eluent to give 2-(4-acetonylphenoxymethyl) -5-hydroxy-4H-pyran-4-one, (1.2g).

'H NMR ($CDCl_3$) ppm:

2.15(3H,s);3.65(2H,s);4.8(2H,s);6.65(1H,s);7.0(4H,dd);7.9(1H,s).

Example X4

Ethyl 3-(4-acetonylphenyl)-2-chloropropionate, ethylene ketal

A solution of ethyl 2-chloroacetoacetate (8.25g) in dry dimethylformamide was treated with sodium hydride (1.3g) and stirred at ambient temperature for 0.5h.A solution of 4-(bromomethyl)phenylpropan-2-one, ethylene ketal (12.0g) in dry dimethylformamide (20ml) was then added and the mixture was heated at 70 °C for 4h. The reaction mixture was cooled, poured into ice/water, acidified with 2N-hydrochloric acid, extracted with ethyl acetate (4x50ml) and the combined organic extracts dried (magnesium sulphate), filtered and evaporated in vacuo. The residue was dissolved in ethanol and treated at 0-5 °C with barium hydroxide hydrate (7.7g). The mixture was stirred for 0.5h, poured into ice/water, extracted with ethyl acetate (3x50ml) and the combined organic extracts dried (magnesium sulphate), filtered and evaporated in vacuo to leave a red oil, which was purified by column chromatography on silica using diethyl ether: petroleum ether (60 °-80 °) (30:70) as eluent to give ethyl 3-(4-acetonylphenyl)-2-chloropropionate, ethylene ketal, (6.0g).

'H NMR ($CDCl_3$)ppm:

1.2(3H,t);1.25(3H,s);2.8(2H,s)3.2(2H,dd);3.8(4H,m);4.2(2H,q) ;4.3(1H,m);7.2(4H,s).

Example X5

5-(4-Acetonylbenzyl)-2-iminothiazolidine-4-one

A mixture of ethyl 3-(4-acetonylphenyl)-2- chloropropionate, ethylene ketal (4.86g), thiourea (1.19g) and sodium acetate (1.29g) in 2-methoxyethanol (25ml) was stirred and heated at 100 °C for 16h. The solvent was evaporated and the residue was diluted with 50:50 water/hexane (50ml). The resulting solid was filtered, dried and purified by chromatography on silica gel. Elution with methanol:chloroform (4:96) gave 5-(4-acetonylbenzyl)-2-iminothiazolidine-4-one as a white solid, mp 196-198 °C.

'H NMR ($CDCl_3$)ppm:

2.20(3H,s);2.95-3.50(2H,m);3.70-4.04(2H,s + 2H, broad, exch.D_2O);4.55 (1H,m);7.20(4H,s).

Example X6

5-(4-Acetonylbenzyl)thiazolidine-2,4-dione

5-(4-Acetonylbenzyl)-2-iminothiazolidine-4-one (1g) was heated under reflux in a mixture of 2-methoxyethanol (20ml) and 2N HCl (5ml) for 8h. The cooled mixture was diluted with water and the resulting precipitate filtered and dried under vacuum to give 5-(4-acetonylbenzyl)thiazolidine-2,4-dione as a white

solid, mp 133-135 °C.

^{1}H NMR ($CDCl_3$)ppm:

2.20(3H,s);3.08-3.55(2H,m);3.72(2H,s);4.55(1H,m);7.27(4H,s); 9.15(1H,broad, exch.D_2O).

Example X7

4-Acetonylphenoxyacetonitrile

A mixture of 4-hydroxyphenylpropan-2-one, ethylene ketal (4.7g), potassium carbonate (3.5g) and chloroacetonitrile (1.83g) in acetone, was heated under reflux for 5h, cooled, filtered, and treated with 2N hydrochloric acid (1ml). The solution was allowed to stand at room temperature for 4h, the solvent was evaporated in vacuo and the residue partitioned between ethylacetate and water. The organic layer was dried, (magnesium sulphate), filtered and evaporated. The residue was purified by column chromatography on silica using chloroform as eluent to give 4-acetonylphenoxyacetonitrile, (3.0g)

^{1}H NMR ($CDCl_3$)ppm:

2.2(3H,s);3.7(2H,s);4.75(2H,s);7.1(4H,dd).

Example X8

4-[2-[(3-Chloro-β-hydroxyphenethyl)amino]propyl] phenoxyacetonitrile

A mixture of 2-(3-chlorophenyl)-2-hydroxyethylamine carbonate (3.35g) and 4-acetonylphenoxyacetonitrile in benzene was heated under reflux for 1h with azeotropic removal of water using a Dean and Stark head. The solution was cooled, and the solvent removed in vacuo. The residue was dissolved in methanol and treated with sodium cyanoborohydride (1.25g) and stirred for 5h at ambient temperature. The solvent was then evaporated under reduced pressure, the residue dissolved in ethyl acetate, washed with water (2x50ml), brine (1x50ml), dried (magnesium sulphate), filtered and evaporated. The residue was purified by column chromatography on silica using methanol:chloroform 2:98 as eluent to give 4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl] phenoxyacetonitrile, (4.0g).

^{1}H NMR ($CDCl_3$)ppm:

0.9(3H,d);2.3-3.0(5H,m);3.0-3.7(2H,m);4.4-4.7(1H,m);4.6(2H,s);6.7-7.4(8H,m).

Example X9

5-(4-Acetonylphenyl)tetrazole

A mixture of 4-cyanophenylacetone (17.0g), ethanediol (6.6g) and 4-toluenesulphonic acid (0.5g) in benzene was heated under reflux with azeotropic removal of water, using a Dean and Stark head, for 18h. The reaction mixture was cooled and the solvent removed in vacuo. The residue was partitioned between ethylacetate and water, the organic layer dried, (magnesium sulphate), filtered and evaporated. The residue was purified by column chromatography on silica using ether: petrol (50:50) as eluent to give 4-cyanophenylacetone, ethylene ketal (11.5g). This material (5g) was dissolved in dry dimethylformamide-(50ml) and treated with sodium azide (1.6g), ammonium chloride (1.34g) and heated at 100 °C for 18h. The solvent was removed in vacuo, the residue dissolved in water, acidified to pH2(HCl) and filtered. The solid material was dissolved in ethyl acetate, dried, (magnesium sulphate), filtered and evaporated. The residue was crystallised from ethanol to give 5-(4-acetonylphenyl)tetrazole, 3.6g.

^{1}H NMR (DMSO-d_6)ppm:

2.2(3H,s);3.85(2H,s);7.35(2H,d);7.95(2H,d);14.8-16.3 (1H, very broad).

Example X10

Methyl 3-(4-acetonylphenyl)-2,3-dibromopropionate ethylene ketal.

A stirred solution of methyl 4-acetonyl cinnamate, ethylene ketal (5.24g) in dry carbon tetrachloride (150ml) at 5 °C, was treated dropwise with a solution of bromine (3.2g) in dry carbon tetrachloride (70ml) over 0.5h. The solution was then washed with 10% sodium hydrogen carbonate solution, dried (magnesium sulphate), filtered and evaporated to dryness to givemethyl 3-(4-acetonylphenyl)-2,3-dibromopropionate, ethylene ketal, (6.4g).

'H NMR ($CDCl_3$) ppm:

1.3(3H,s);2.9(2H,s);3.8(4H,m);3.9(3H,s);4.8(1H,d); 5.4(1H,d);7.3(4H,s).

Example X11

5-(4-Acetonylphenyl)-3-hydroxyisoxazole

A solution of methyl 3-(4-acetonylphenyl)-2,3-dibromo-propionate, ethylene ketal (4.2g) in methanol (25ml) was added dropwise to a stirred mixture of hydroxylamine hydrochloride (0.86g) and potassium hydroxide (3.9g) in methanol: water (150ml) at ambient temperature and stirred for 1h. The reaction mixture was then heated under reflux for 7h, cooled, acidified with sulphuric acid (50%), filtered, and the solvent removed under reduced pressure. The residue was partitioned between ethylacetate and water, dried (magnesium sulphate), filtered and evaporated to dryness in vacuo. The residue was as eluent, and crystallised from diethylether-(60-80 °)petroleum ether to give 5-(4-acetonylphenyl)-3-hydroxyisoxazole (0.5g).

'H NMR ($CDCl_3$ + CD_3OD)ppm:

2.25(3H,s);3.8(2H,s);4.6(1H,s);6.2(1H,s);7.3(2H,d); 7.8(2H,d).

Example X12

(4-Acetonylphenoxy)-3-aminopropan-2-ol, ethylene ketal.

A solution of (4-hydroxyphenyl)propan-2-one, ethylene ketal (30g) in ethanol (50ml) was added to a solution of sodium hydroxide (6.18g) in ethanol (100ml). The resulting solution was added, over 30 minutes, to a stirred solution of epichlorohydrin (39.66g) in dioxan (180ml) and water (45ml) maintained at 75-80 °C. The mixture was stirred at 75-80 °C for a further hour after the addition was complete, cooled and filtered. The filtrate was evaporated to an oil which was partitioned between dichloromethane and water. The organic phase was dried and evaporated to an oil which was dissolved in ethanol (600ml) containing six pellets of sodium hydroxide and treated with 0.88 ammonia solution (600ml) enriched with ammonia gas. The resulting solution was shaken at ambient temperature in a sealed flask for 20 hrs. The solvent was evaporated to give a waxy solid. Recrystallisation from isopropanol/ether gave (4-acetonylphenoxy)-3-aminopropan-2-ol, ethylene ketal as pale yellow solid.

^1H NMR ($CDCl_3$) ppm:

1.30(s,3H); 2.45(s,3H replaceable by D_2O); 2.80-3.05(m,4H); 3.75-4.05(m,7H); 6.75-7.30(q,4H).

Example X13

Ethyl[N-[4-[2-[(3-chloro-β-hydroxyphenyl)amino]propyl]phenyl]-N-carbomethoxymethyl]malonamide.

A mixture of 2-(3-chlorophenyl)-2-hydroxyethanamine carbonate (0.135g, 0.33mmol) and ethyl[N-(4-acetonylphenyl)-N-carbomethoxymethyl]malonamide (0.230g, 0.69mmol) in benzene (15ml) was heated in a Dean and Stark apparatus for 2 hr. The resulting solution was cooled, concentrated in vacuo and the residue dissolved in ethanol (10ml). Sodium cyanoborohydride (0.052g, 0.86mmol) was added and the solution

stirred for 16 hr. The solvent was evaporated and the resulting oil was partitioned between ethylacetate and water. The organic fraction was separated, dried (magnesium sulphate) and the solvent evaporated to give an oil which was chromatographed on Silica. Elution with 95:5 chloroform/ethanol gave ethyl-[N-[4-[2-[(3-chloro-β-hydroxyphenyl)amino]propyl]phenyl]-N-carbomethoxymethyl]malonamide as a colourless oil (0.29g; 88%).

^{1}H NMR ($CDCl_3$) ppm:

1.0-1.3(6H,m); 2.45-3.0(6H,m); 3.1(2H,s); 3.65(3H,s); 4.0(2H,q); 4.25(2H,s); 4.4(2H,br hump); 7.2(8H,m).

Example X14

Ethyl[N-(4-acetonylphenyl)-N-carbomethoxymethyl]malonamide.

A solution of methyl N-(4-acetonylphenyl) glycinate, ethylene ketal (1.51g, 6mmol) in methylene chloride (30ml) was cooled to 0°C under an atmosphere of nitrogen. Triethylamine (1ml, 7.5mmol) was added to the solution followed by the dropwise addition of ethyl malonyl chloride (0.77ml, 6mmol) over 15 minutes. The mixture was stirred for 1 hr., poured into 2N HCl (50ml) and the mixture stirred vigorously for 3 hr. The organic fraction was separated, washed with saturated sodium bicarbonate solution, dried (magnesium sulphate), concentrated in vacuo and the residue chromatographed on Silica. Elution with petroleum ether/ether (1:2) gave ethyl[N-(4-acetonylphenyl)-N-carbomethoxymethyl]malonamide (0.77g, 41%) as a colourless oil.

^{1}H NMR ($CDCl_3$) ppm:

1.2(3H,t); 2.2(3H,s); 3.25(2H,s); 3.75(3H,s); 4.05(2H,q); 4.4(2H,s); 7.35(5H, br.s).

Example X15

Methyl N-[4-acetonylphenyl]glycinate, ethylene ketal.

4-Aminophenylpropan-2-one, ethylene ketal (10.90g, 0.06mol) in benzene (150ml) was heated with methyl glyoxalate (6.14g, 0.07mol) in a Dean and Stark apparatus for 1 hr. The solution was allowed to cool, concentrated in vacuo and the residue dissolved in methanol (150ml). Sodium cyanoborohydride (4.06g 0.068mol) was added portionwise over 0.5 hr. and the resulting mixture stirred for 16 hr. Evaporation of the solvent gave an oil which was partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$) and evaporated to give an oil which was chromatographed on Silica. Elution with an ethyl acetate/petroleum ether mixture (1:1) provided methyl N-[4-acetonylphenyl]glycinate, ethylene ketal (10.37g, 68%) as an oil.

^{1}H NMR ($CDCl_3$) ppm:

1.3(3H,s); 2.8(2H,s); 3.7-4.3(8H,m); 6.55(2H,d); 7.15(2H,d)

Example X16

5-(4-Acetonylphenoxymethyl)-3-hydroxyisoxazole

A solution of (4-hydroxyphenyl)propan-2-one ethylene ketal (1.4g) in ethanol, was treated with a solution of sodium (0.16g) in ethanol (25ml) and heated under reflux for 10 minutes. A solution of 5-chloromethyl-2-(1,2,3,4-tetrahydropyran-2-yl)isoxazol-3-(2H)one (1.5g) in ethanol was added dropwise, and the reaction was heated for 18 hr. The cooled solution was evaporated in vacuo, the residue partitioned between ethylacetate and water, the organic layer separated, dried (magnesium sulphate), and the solvent removed in vacuo to give an oil which was chromatographed on silica. Elution with ether: 60:80 petrol (1:1) gave an oil which was dissolved in acetone and treated with 2M hydrochloric acid solution (5ml) and allowed to stand at room temperature for 4 hr. The solvent was removed in vacuo, the residue dissolved in ethyl acetate, washed with 1.2M sodium bicarbonate solution (1x50ml), dried (magnesium sulphate), filtered and evaporated to give 5-(4-acetonylphenoxymethyl)3-hydroxyisoxazole.

^{1}H NMR ($CDCl_3$) ppm.

2.2 (3H,s); 3.7(2H,s); 4.9 (1H,s); 5.0 (2H,s) 6.0 (1H,s); 6.9-7.4 (4H,dd).

Demonstration of Effectiveness of Compounds

(I) Anti-obesity Activity.

(a) The test compound was administered by oral gavage in water to genetically obese mice daily for 28 days. At the end of the time the carcass composition was determined. The result obtained was as follows:

Compound of Example No.	Dose mg/Kg p.o	g lipid/mouse	
		treated	control
3	8.6	19.40	23.63

(b) Female BALB/c mice were trained to feed on powdered oxoid for 1 week. They were then housed in threes and the compound under study was added to the diet for 3 days. Food was removed at 09.00h and the mice were killed at 11.00h. The parametrial fat pads were weighed as pairs. The result is a mean of 9 values.

Compound of Example No.	Dose mg/kg diet	Percentage reduction in weight of parametrial fat pads compared with controls
1	85	40
3	64	22
4	200	11
6	94	13
7	62	6
9	112	45
13	81	30

(II) Effect on energy expenditure of mice

The effect of the compounds on the energy expenditure of mice was demonstrated by means of the following procedure:
Female CFLP mice each weighing approximately 24g were given food and water ad lib before and during the experiment. The compounds were dissolved in water by addition of one mole of hydrochloric acid per mole of compound and these solutions were administered orally to each of 12 mice. A further 12 mice were dosed orally with water. The mice were placed in boxes through which air was drawn and the oxygen content of the air leaving the boxes was measured. The energy expenditure of the mice was calculated for 21 hours after dosing from the volume of air leaving the boxes and its oxygen content, following the principles described by J.B. de V. Weir, J. Physiol. (London) 109, 1-9 (1949). The results are expressed as a percentage of the rate of energy expenditure of the mice dosed with water.

Compounds of Example No.	Dose mg/kg p.o.	Mean Energy Expenditure	
		(0-3h)	(0-21h)
1	8.3	110	93
3	8.6	136	115
9	7.8	126	117

(III) Effect on Energy Expenditure of Rats

The effect of the compounds on the energy expenditure of rats was demonstrated by means of the followingprocedure:

Male Sprague-Dawley rats each weighing between 170-200 g were deprived of food for 16 hours before,and during the experiment. Water was provided ad lib at all times. The compounds were administered orally in water to 3 or 4 rats. A further 4 rats were dosed orally with water. The rats were placed in boxes through which air was drawn and the oxygen content of the air leaving the boxes was measured. The energy expenditure of the rats was calculated for 3 hours and for 21 hours after dosing from the volume of air leaving the boxes and its oxygen content, following the principles described by J.B. de V. Weir, J. Physiol. (London) 109, 1-9 (1949). The results are expressed as a percentage of the rate of energy expenditure of the rats dosed with water.

Compound of Example No.	Dose mg/kg p.o.	Mean Energy Expenditure	
		(0-3h)	(0-21h)
1	4.25	125	115
2	4.16	116	106
3	8.6	137	131
4	20.0	108	103
5	4.3	137	120
6	4.7	138	111
7	20.7	121	113
8	18.1	118	110
9	7.55	117	114
10	8.22	130	110
11	9.59	121	128
12	9.50	112	110
13	8.00	134	112
14	4.86	108	107

(IV) Hypoglycaemic activity

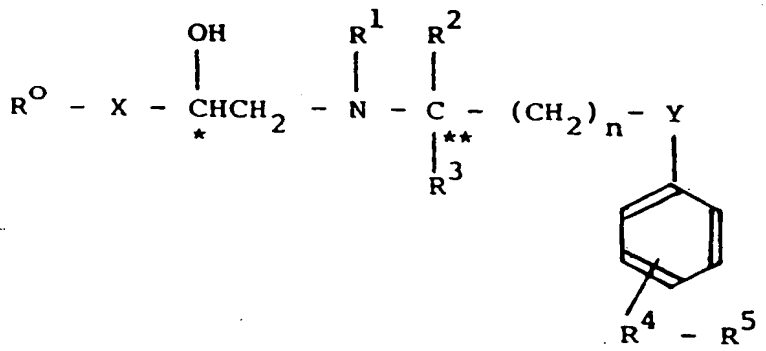
Female CFLP mice, weighing approximately 25 g, were fasted for 24 hours prior to the study. The compounds under study were administered orally as an aqueous solution to each of the 6 mice. 30 minutes later a blood sample (20µl) was obtained from the tail for the analysis of blood glucose. Immediately after taking this blood sample, glucose (1 g/kg body weight) was administered subcutaneously to each mouse. 6 mice were given water as a control. Blood samples were then obtained from each mouse at 30 minute intervals for 120 minutes.

Compounds that produced a significant ($p<0.05$) reduction of blood glucose, compared with control mice given water, at any time interval, were considered active. The area under the blood glucose curve over the 2 hour period after the administration of the glucose was calculated for each compound and compared with the value for control animals.

Compounds of Example No.	Dose µmol/kg	% Reduction in Area under Blood Glucose Curve
1	2.5	44
4	25	11
5	2.5	39
6	12.5	9
7	1.0	47
8	1.0	45
9	2.5	28

Claims

1. A compound of the general formula (I):

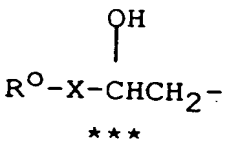


or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, wherein,

R^o represents a phenyl or napthyl group optionally substituted with up to five groups selected form halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy alkyl, hydroxy, amino, nitro, carboxy and pharmaceutically acceptable salts, esters and amides thereof, alkoxycarbonyl, alkoxycarbonyl alkyl alkylcarbonyloxy, or alkylcarbonyl groups; or a benzofuranyl group optionally substituted in the phenyl ring with an alkyl group;

X represents a bond or $-O-CH_2-$,

R^1 represents a hydrogen atom or a moiety



wherein R^0 and X are as defined above;

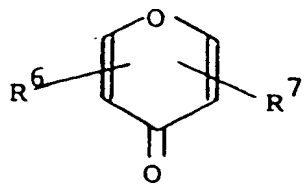
R^2 and R^3 independently represent a hydrogen atom or an alkyl group,

n represents an integer 1 or 2,

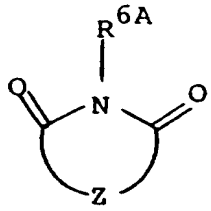
Y represents a bond or a moiety $-CH_2-O-$,

R^4 represents a bond or an oxygen atom or $-R^{4A}$ or a moiety $-O-R^{4A}-$ or a moiety $-R^{4A}-O-$, wherein R^{4A} represents a $-CH_2-$group,an alkenylene group or a alkynylene group; and

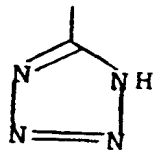
R^5 represents a group of the general formulae (A), (B), (C) or (D):



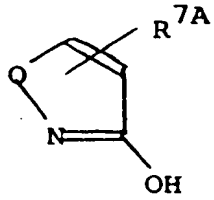
(A)



(B)

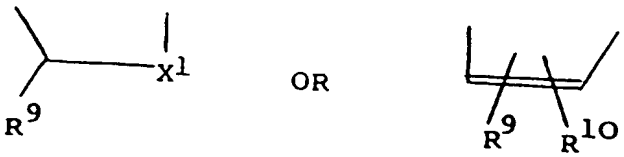


(C)



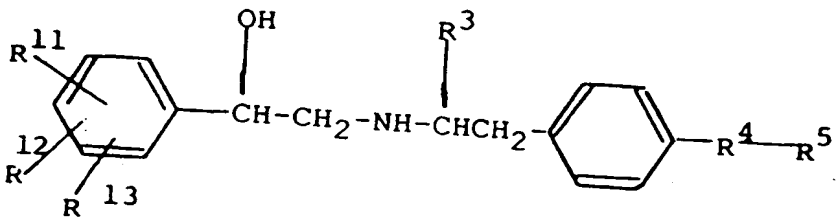
(D)

wherein R^6 and R^7 each independently represent a bond, a hydrogen atom, a hydroxyl group, an alkyloxy group; or a benzyloxy group; R^{6A} represents a bond or a hydrogen atom or an alkyl group or a carbonylalkyl group; R^{7A} represents a bond; and Z represents a moiety of formula:



wherein R^9 and R^{10} each independently represent a bond, a hydrogen atom, a hydroxyl group, an alkoxy group; and X^1 represents O, NH or S; provided that at least one of R^6 and R^7; and at least one of R^{6A}, R^9 and R^{10} represents a bond.

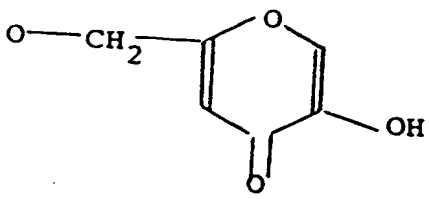
2. A compound as claimed in claim 1, characterized in that it is represented by formula (II):



(II)

or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof, wherein R^3, R^4 and R^5 are as defined above and R^{11}, R^{12} and R^{13} each independently represent hydrogen; halogen, preferably chlorine; amino, hydroxy or hydroxymethyl.

3. A compound as claimed in claim 1 or claim 2, characterized in that the moiety $-R^4-R^5-$ represents:



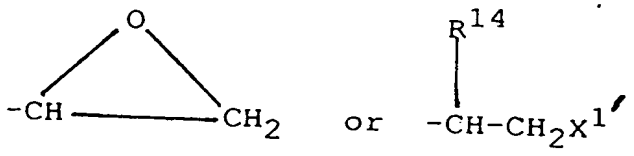
4. A compound as claimed in claim 1, characterized in that it is selected from the group consisting of:
4-[4-[2-[(3-chloro-β-hydroxyphenethyl) amino]propyl]phenoxy]-3-hydroxy-1H-pyrrole-2,5-dione;
4-[4-[2-[(β,4-dihydroxyphenethyl)amino]propyl]phenoxy]-3-hyd roxy-1H-pyrrole-2,5-dione;
2-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]phenoxymethyl]-5-hydroxy-4H-pyran-4-one;
5-[4-(2-[(β-4-dihydroxyphenethyl)amino]propyl]benzyl] thiazolidine-2,4-dione;
5-[4-[2-[(3-chloro-β-hydroxyphenethyl)amino]propyl]benzyl]thiazolidine-2,4-dione;
5-[4-[2-[(4-amino-3,5-dichloro-β-hydroxyphenethyl) amino]propyl]benzyl]thiazolidine-2,4-dione;
5-[4-[2-[3-chloro-β-hydroxyphenethyl)amino]propyl] -phenoxymethyl]tetrazole;
5-[4-[2-(3-chloro-β-hydroxyphenethyl)amino]propyl] phenyl]tetrazole; and
5-[4-[2-(3-chloro-β-hydroxyphenethyl)amino]propyl] phenyl]-3-hydroxyisoxazole; or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof.

5. A process for preparing a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable ester; or a pharmaceutically acceptable salt thereof, characterized in that the process comprises:

(A) reacting a compound of the general formula (III)

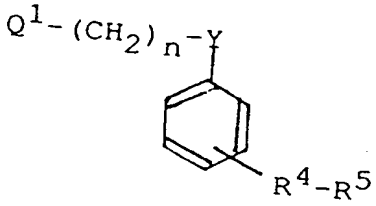
R^o-X-Q (III)

wherein R^o and X are as defined in relation to formula (I) and Q represents a group of formula (a) or (b):



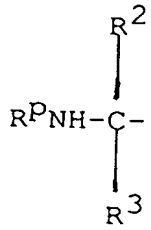
(a) (b).

wherein
R^{14} represents a hydroxyl group or a protected hydroxyl group, and $X^{1'}$ represents a leaving group, with a compound of the general formula (IV):



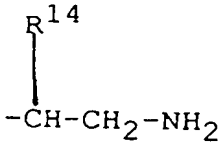
(IV)

wherein R^4, R^5, n and Y are as defined in relation to formula (I), and
Q^1 represents a group of the formula (F):



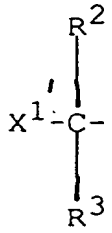
(F)

wherein R^2 and R^3 are as defined in relation to formula (I), and R^p represents a hydrogen atom, a protecting group, preferably a benzyl group, or the hereinbefore defined moiety R^1;
or in the abovementioned compound of formula (III) Q represents a group of the formula (c):



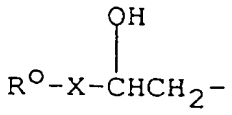
(c)

wherein R^{14} has the meaning given above, and in the abovementioned compound of formula (IV) Q^1 represents a group of the formula (g):



(g)

in which R^2, R^3 and $X^{1'}$ have the meanings given above; or
(B) for compounds of formula (I) wherein R^1 represents only the moiety



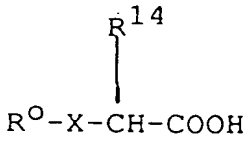
as defined above, by reacting a compound of formula (I) wherein R^1 represents a hydrogen atom, with either:
(i) a compound of formula (IIIA):

R^o-X-Q (IIIA)

wherein R^o and X are as defined in relation to formula (I) and Q represents a group of the hereinbefore defined formula (a) or (b); or
(ii) a compound of formula (V):

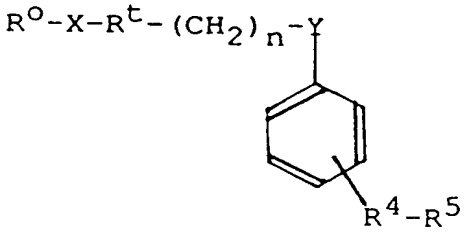
R^o-X-CO-CHO (V)

wherein R^o and X are as defined in relation to formula (I); and subsequently treating with a reducing agent; or
(iii) a compound of formula (VI):



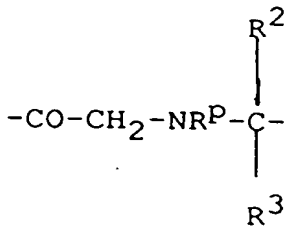
(VI)

wherein R^o and X are as defined in relation to formula (I) and R^{14} represents a hydroxyl group or a protected hydroxyl group; or
comprises reducing a compound of the general formula (VII):

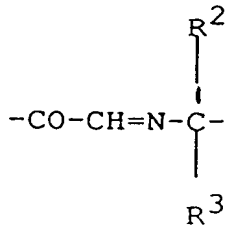


(VII)

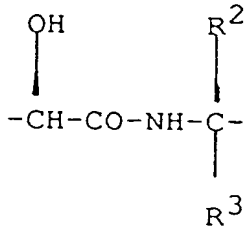
in which
R^o, R^4, R^5, X, Y and n are as defined in relation to formula (I), and R^t represents a group of formula:



(i),

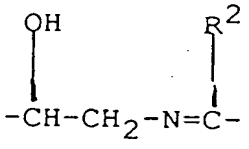


(ii),



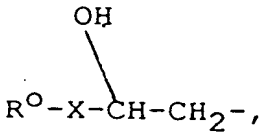
(iii),

or



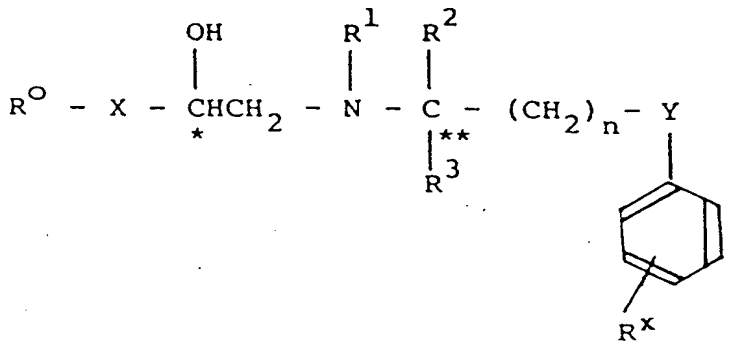
(iv)

in which R^P is hydrogen or a protecting group,
preferably a benzyl group, R^2 and R^3 are as defined in relation to formula (I);
and if required converting a compound of formula (I) wherein R^1 represents hydrogen into a compound of formula (I) wherein R^1 represents a moiety of formula



wherein R^o and X are as defined above, by reacting the compound of formula (I) wherein R^1 represents hydrogen with a compound of formula (IIIA), (V) or (VI) as described hereinbefore; or

(C) from a compound of formula (VIII):



(VIII)

wherein R^0, R^1, R^2, R^3, X, n and Y are as defined in relation to formula (I) and R^x is a moiety convertible to a moiety $-R^4-R^5$;

and thereafter if necessary carrying out one or more of the following steps;

i) removing any protecting group;

ii) converting a compound of formula (I) into a further compound of formula (I);

iii) converting a salt of formula (I) into a free compound of formula (I);

iv) preparing a pharmaceutically acceptable ester of a compound of formula (I);

v) preparing a pharmaceutically acceptable salt of a compound of formula (I) or an ester thereof.

6. A pharmaceutical composition comprising a compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

7. A compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable ester; or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

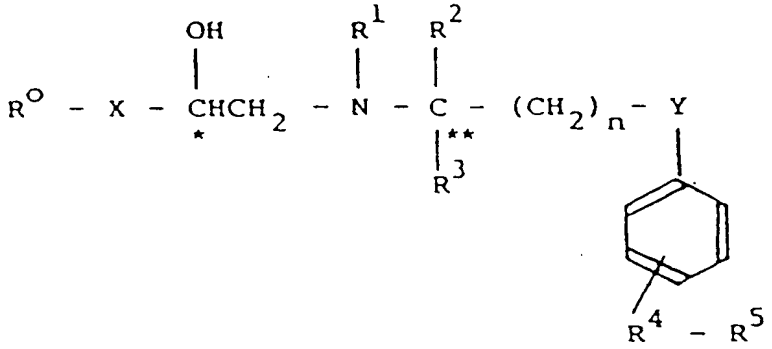
8. A compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof for use in the treatment of obesity and/or hyperglycaemia in human or non-human animals.

9. The use of a compound of formula (I), or a pharmaceutically acceptable ester thereof; or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of obesity or hyperglycaemia.

10. A method for increasing weight gain and/or improving the feed utilisation efficiency and/or increasing lean body mass of livestock, which method comprises the administration to livestock of an effective non-toxic amount of a compound of formula (I) or a veterinarily acceptable ester thereof; or a veterinarily acceptable salt thereof.

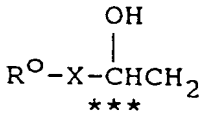
Patentansprüche

1. Verbindung der allgemeinen Formel (I)

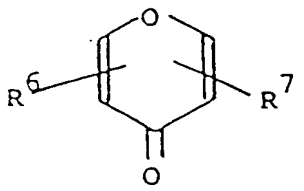


(I)

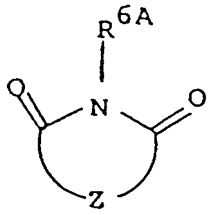
oder ein pharmazeutisch verträglicher Ester davon, oder ein pharmazeutisch verträgliches Salz davon, wobei
R^o eine Phenyl- oder Naphthylgruppe; gegebenenfalls substituiert mit bis zu fünf Resten, ausgewählt aus Halogenatomen, Alkyl-, Phenyl-, Alkoxy-, Halogenalkyl-, Hydroxyalkyl-, Hydroxy-, Amino-, Nitro-, Carboxyresten und pharmazeutisch verträglichen Salzen, Estern und Amiden davon, Alkoxycarbonyl-, Alkoxycarbonylalkyl, Alkylcarbonyloxy- oder Alkylcarbonylresten; oder eine Benzofuranylgruppe, gegebenenfalls am Phenylring mit einem Alkylrest substituiert, bedeutet;
X eine Bindung oder die Gruppe $-O-CH_2-$ darstellt,
R^1 ein Wasserstoffatom oder einen Rest der Formel



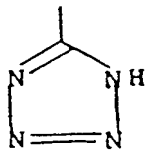
bedeutet, in der R^o und X wie vorstehend definiert sind,
R^2 und R^3 unabhängig voneinander ein Wasserstoffatom oder einen Alkylrest darstellen,
n eine ganze Zahl im Wert von 1 oder 2 darstellt,
Y eine Bindung oder die Gruppe $-CH_2-O-$ bedeutet,
R^4 eine Bindung oder ein Sauerstoffatom oder $-R^{4A}$ oder einen Rest $-O-R^{4A}-$ oder einen Rest $-R^{4A}-O-$ darstellt, wobei R^{4A} eine $-CH_2-$Gruppe, einen Alkenylenrest oder einen Alkinylenrest darstellt und
R^5 einen Rest der allgemeinen Formeln (A), (B), (C) oder (D) bedeutet:



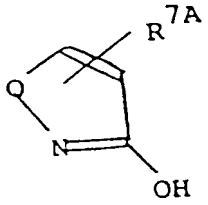
(A)



(B)

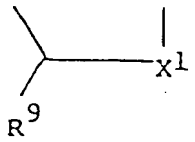


(C)

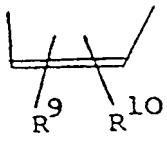


(D)

in denen R^6 und R^7 unabhängig voneinander eine Bindung, ein Wasserstoffatom, eine Hydroxylgruppe, einen Alkyloxyrest oder eine Benzyloxygruppe bedeuten; R^{6A} eine Bindung oder ein Wasserstoffatom oder einen Alkylrest oder einen Carbonylalkylrest darstellt, R^{7A} eine Bindung bedeutet; und Z einen Rest der Formel:

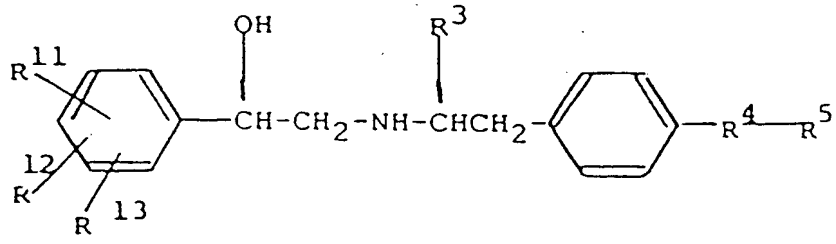


oder



darstellt, wobei R^9 und R^{10} jeweils unabhängig voneinander eine Bindung, ein Wasserstoffatom, eine Hydroxylgruppe oder einen Alkoxyrest darstellen und X^1 O, NH oder S darstellt; mit der Maßgabe, daß mindestens einer der Reste R^6 und R^7 und mindestens einer der Reste R^{6A}, R^9 und R^{10} eine Bindung darstellen.

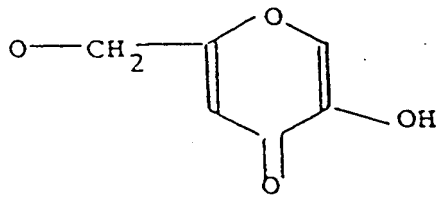
2. Verbindung nach Anspruch 1 der Formel (II):



(II)

oder ein pharmazeutisch verträglicher Ester davon oder ein pharmazeutisch verträgliches Salz davon, wobei R^3, R^4 und R^5 wie vorstehend definiert sind, und R^{11}, R^{12} und R^{13} jeweils unabhängig voneinander ein Wasserstoffatom, ein Halogenatom, vorzugsweise ein Chloratom, eine Amino-, Hydroxy- oder Hydroxymethylgruppe darstellen.

3. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß der Rest -R^4-R^5- durch die Formel



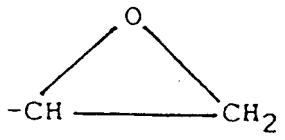
wiedergegeben wird.

4. Verbindung nach Anspruch 1, nämlich
4-[4-[2-[(3-Chlor-β-hydroxyphenethyl)-amino]-propyl]phenoxy]-3-hydroxy-1H-pyrrol-2,5-dion;
4-[4-[2-[(β,4-Dihydroxyphenethyl)amino]propyl]phenoxy]-3-hydroxy-1H-pyrrol-2,5-dion;
2-[4-[2-[(3-Chlor-β-hydroxyphenethyl)amino]propyl]-phenoxymethyl]-5-hydroxy-4H-pyran-4-on;
5-[4-[2-[(β-4-Dihydroxyphenethyl)amino]propyl]benzyl]thiazolidin-2,4-dion;
5-(4-[2-[(3-Chlor-β-hydroxyphenethyl)amino]propyl]-benzyl]thiazolidin-2,4-dion;
5-[4-[2-[(4-Amino-3,5-dichlor-β-hydroxyphenethyl)amino]propyl]benzyl]thiazolidin-2,4-dion;
5-(4-[2-[3-Chlor-β-hydroxyphenethyl)amino]propyl]-phenoxymethyl]tetrazol;
5-[4-[2-(3-Chlor-β-hydroxyphenethyl)amino]propyl]-phenyl]tetrazol; oder
5-[4-[2-(3-Chlor-β-hydroxyphenethyl)amino]propyl]-phenyl]-3-hydroxyisoxazol; oder ein pharmazeutisch verträglicher Ester davon oder ein pharmazeutisch verträgliches Salz davon.

5. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch verträglichen Esters oder eines pharmazeutisch verträglichen Salzes davon, dadurch gekennzeichnet, daß das Verfahren umfaßt:
(A) Umsetzen einer Verbindung der allgemeinen Formel (III)

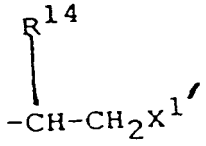
R^o-X-Q (III)

in der R^o und X wie in Formel (I) definiert sind und Q eine Gruppe der Formel (a) oder (b) bedeutet:



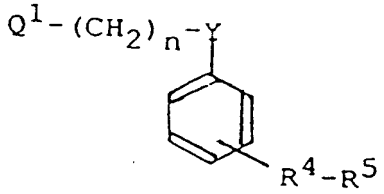
(a)

oder



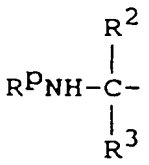
(b)

wobei R^{14} eine Hydroxylgruppe oder eine geschützte Hydroxylgruppe darstellt und $X^{1'}$ eine Austrittsgruppe bedeutet, mit einer Verbindung der allgemeinen Formel (IV):



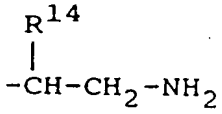
(IV)

in der R^4, R^5, n und Y wie in Formel (I) definiert sind und
Q^1 eine Gruppe der Formel (F) bedeutet:



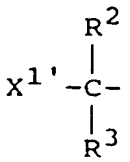
(F)

in der R^2 und R^3 wie in Formel (I) definiert sind und R^p ein Wasserstoffatom, eine Schutzgruppe, vorzugsweise eine Benzylgruppe, oder einen hier vorstehend definierten Rest R^1 bedeutet;
oder in der vorstehend genannten Verbindung der Formel (III) Q eine Gruppe der Formel (c) darstellt:



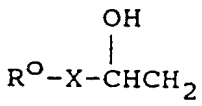
(c)

in der R^{14} die vorstehend angegebene Bedeutung aufweist, und in der vorstehend genannten Verbindung der Formel (IV) Q^1 eine Gruppe der Formel (g) bedeutet:



(g)

in der R^2, R^3 und $X^{1'}$ die vorstehend genannten Bedeutungen aufweisen, oder
(B) für Verbindungen der Formel (I), in denen R^1 nur den Rest der Formel



wie vorstehend definiert, bedeutet, durch Umsetzen einer Verbindung der Formel (I), in der R^1 ein Wasserstoffatom bedeutet, mit entweder

(i) einer Verbindung der Formel (IIIA)

R^o-X-Q (IIIA)

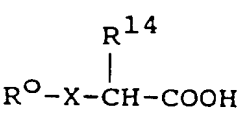
in der R^o und X wie in Formel (I) definiert sind, und Q einen Rest der hier vorstehend definierten Formel (a) oder (b) darstellt; oder

(ii) einer Verbindung der Formel (V):

R^o-X-CO-CHO (V)

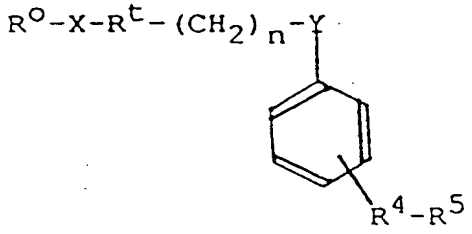
in der R^o und X wie in der Formel (I) definiert sind, und anschließendes Behandeln mit einem Reduktionsmittel, oder

(iii) einer Verbindung der Formel (VI):



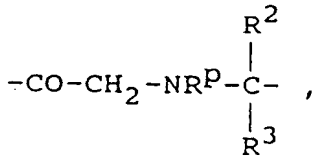
(VI)

in der R^o und X wie in Formel (I) definiert sind und R^{14} eine Hydroxylgruppe oder eine geschützte Hydroxylgruppe bedeutet; oder
umfassend das Reduzieren einer Verbindung der allgemeinen Formel (VII)

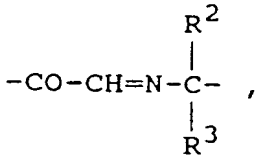


(VII)

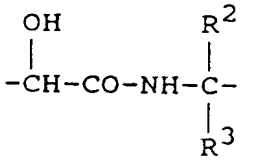
in der R^o, R^4, R^5, X, Y und n wie in der Formel (I) definiert sind und R^1 einen Rest der Formel:



(i)

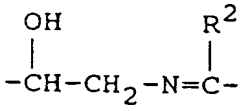


(ii)



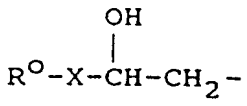
(iii)

oder



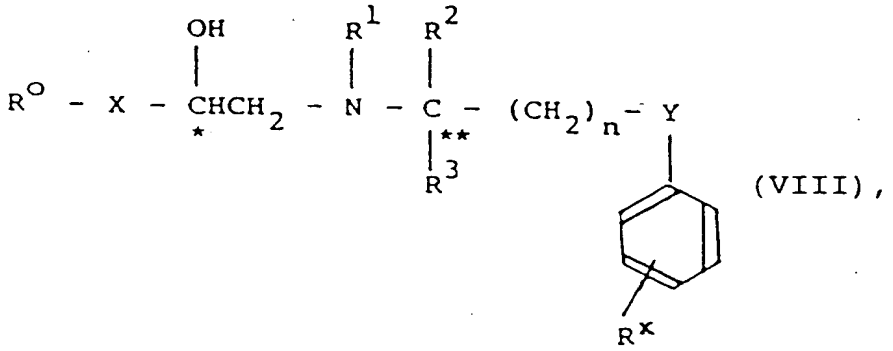
(iv)

bedeutet, in denen R^p ein Wasserstoffatom oder eine geschützte Gruppe darstellt, vorzugsweise eine Benzylgruppe, R^2 und R^3 wie in Formel (I) definiert sind;
und falls erforderlich, Umwandeln einer Verbindung der Formel (I), in der R^1 ein Wasserstoffatom darstellt, in eine Verbindung der Formel (I), in der R^1 einen Rest der Formel



bedeutet, in der R^o und X wie vorstehend definiert sind, durch Umsetzen der Verbindung der Formel (I), in der R^1 ein Wasserstoffatom bedeutet, mit einer Verbindung der Formel (IIIA), (V) oder (VI) wie vorstehend beschrieben, oder

(C) aus einer Verbindung der Formel (VIII):



(VIII),

in der R^o, R^1, R^2, R^3, X, n und Y wie in Formel (I) definiert sind und R^x einen in einen Rest $-R^4-R^5$ umwandelbaren Rest bedeutet;
und anschließend, falls erforderlich, Ausführeneines oder mehrerer der nachstehenden Schritte;

i) Entfernen einer Schutzgruppe;
ii) Umwandeln einer Verbindung der Formel (I) in eine weitere Verbindung der Formel (I);
iii) Umwandeln eines Salzes der Formel (I) in eine freie Verbindung der Formel (I);
iv) Herstellen eines pharmazeutisch verträglichen Esters einer Verbindung der Formel (I);
v) Herstellen eines pharmazeutisch verträglichen Salzes einer Verbindung der Formel (I) oder eines Esters davon.

6. Arzneimittel, umfassend eine Verbindung der allgemeinen Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch verträglichen Esters davon oder eines pharmazeutisch verträglichen Salzes davon und einen pharmazeutisch verträglichen Träger dafür.

7. Verbindung der allgemeinen Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch verträglichen Esters oder eines pharmazeutisch verträglichen Salzes davon zur Verwendung als therapeutischer Wirkstoff.

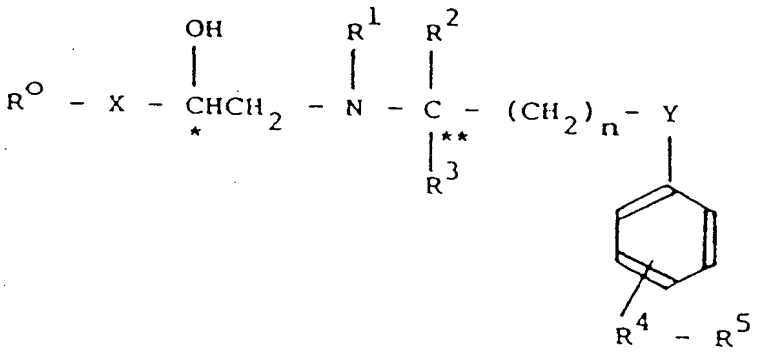
8. Verbindung der allgemeinen Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch verträglichen Esters davon oder eines pharmazeutisch verträglichen Salzes davon, zur Verwendung bei der Behandlung von Fettsucht und/oder Hyperglykämie bei Menschen oder nicht-menschlichen Tieren.

9. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Esters davon oder eines pharmazeutisch verträglichen Salzes davon, für die Herstellung eines Arzneimittels zur Behandlung von Fettsucht oder Hyperglykämie.

10. Verfahren zur Erhöhung der Gewichtszunahme und/oder Verbesserung der Futterverwertung und/oder Erhöhung der fettfreien Körpermasse von Vieh, umfassend die Verabreichung einer wirksamen nichttoxischen Menge einer Verbindung der Formel (I) oder eines tierarzneilich verträglichen Esters davon oder eines tierarzneilich verträglichen Salzes davon an das Vieh.

Revendications

1. Composé de formule générale (I):



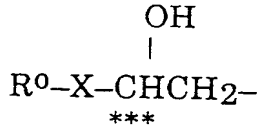
(I)

ou ester de celui-ci acceptable du point de vue pharmaceutique, ou sel de celui-ci acceptable du point de pharmaceutique,
dans laquelle :

R^o représente un groupe phényle ou naphtyle éventuellement substitué avec un maximum de cinq groupes choisis parmi un atome d'halogène, un groupe alkyle, phényle, alcoxy, haloalkyle, hydroxyalkyle, hydroxy, amino, nitro, carboxy et ses sels, esters et amides acceptables du point de vue pharmaceutique, alcoxycarbonyle, alcoxycarbonyl alkyl alkylcarbonyloxy ou alkylcarbonyle; ou un groupe benzofuranyle dont le cycle phényle est éventuellement substitué par un groupe alkyle;

X représente une liaison ou un radical $-O-CH_2-$,

R^1 représente un atome d'hydrogène ou une partie



dans laquelle R^o et X sont tels que définis plus haut;

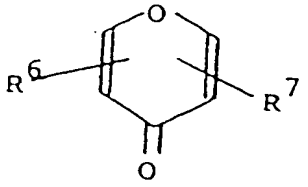
R^2 et R^3 sont indépendamment un atome d'hydrogène ou un groupe alkyle,

n représente un entier de 1 ou 2,

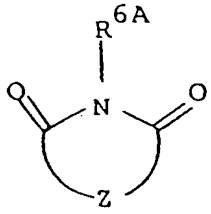
Y représente une liaison ou un radical $-CH_2-O-$,

R^4 représente une liaison ou un atome d'oxygène ou $-R^{4A}$ ou un radical $-O-R^{4A}-$ ou une partie $-R^{4A}-O-$, dans laquelle R^{4A} représente un groupe $-CH_2-$, un groupe alcénylène ou un groupe alcynylène; et

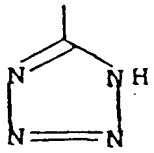
R^5 représente un groupe de formule générale (A), (B), (C) ou (D) :



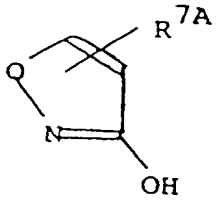
(A)



(B)

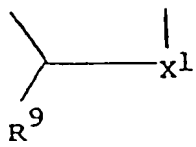


(C)

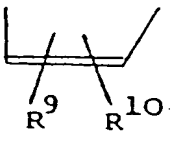


(D)

dans lesquelles R^6 et R^7 représentent indépendamment une liaison, un atome d'hydrogène, un groupe hydroxy, un groupe alkyloxy; ou un groupe benzyloxy; R^{6A} représente une liaison ou un atome d'hydrogène ou un groupe alkyle ou un groupe carbonylalkyle; R^{7A} représente une liaison; et Z représente une partie de formule :

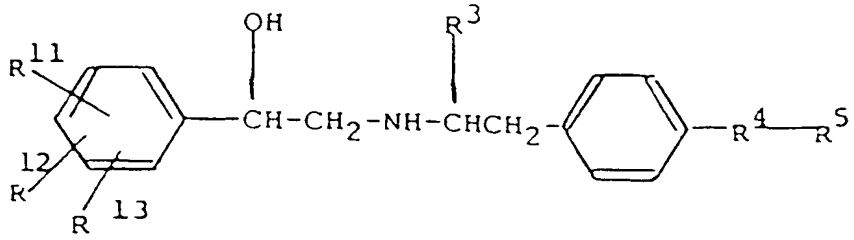


ou



dans lesquelles R^9 et R^{10} représentent chacun une liaison, un atome d'hydrogène, un groupe hydroxy, un groupe alcoxy, et X^1 représente O, NH ou S; à condition qu'au moins l'un des R^6 et R^7, et ou moins l'un des R^{6A}, R^9 et R^{10} représente une liaison.

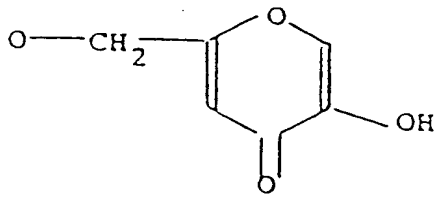
2. Composé suivant la revendication 1, caractérisé en ce qu'il est représenté par la formule (II) :



(II)

ou ester de celui-ci acceptable du point de vue pharmaceutique, ou sel de celui-ci acceptable du point de pharmaceutique, dans laquelle R^3, R^4 et R^5 sont tels que définis plus haut, et R^{11}, R^{12} et R^{13} sont chacun indépendamment un atome d'hydrogène; un atome d'halogène, de préférence de chlore; un groupe amino, hydroxy ou hydroxyméthyle.

3. Composé suivant les revendications 1 ou 2, caractérisé en ce que la partie $-R^4-R^5-$ représente :

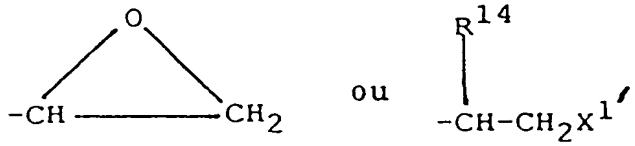


4. Composé suivant la revendication 1, caractérisé en ce qu'il est choisi dans le groupe consistant en :
4-[4-[2-[(3-chloro-β-hydroxyphénéthyl)-amino]-propyl]-phénoxy]-3-hydroxy-1H-pyrrole-2,5-dione;
4-[4-[2-[(β,4-dihydroxyphénéthyl)-amino]-propyl]-phénoxy]-3-hydroxy-1H-pyrrole-2,5-dione;
2-[4-[2-[(3-chloro-β-hydroxyphénéthyl)-amino]-propyl]-phénoxyméthyl]-5-hydroxy-4H-pyran-4-one;
5-[4-[2-[(β,4-dihydroxyphénéthyl)-amino]-propyl]-benzyl]-thiazolidine-2,4-dione;
5-[4-[2-[(3-chloro-β-hydroxyphénéthyl)-amino]-propyl]-benzyl]-thiazolidine-2,4-dione;
5-[4-[2-[(4-amino-3,5-dichloro-β-hydroxyphénéthyl)-amino]-propyl]-benzyl]-thiazolidine-2,4-dione;
5-[4-[2-[(3-chloro-β-hydroxyphénéthyl)-amino]-propyl]-phénoxyméthyl]-tétrazole;
5-[4-[2-[(3-chloro-β-hydroxyphénéthyl)-amino]-propyl]-phényl]-tétrazole; et
5-[4-[2-[(3-chloro-β-hydroxyphénéthyl)-amino]-propyl]-phényl]-3-hydroxrisoxazole;
ou un ester de ceux-ci acceptable du point de vue pharmaceutique, ou un sel de ceux-ci acceptable du point de pharmaceutique.

5. Procédé pour préparer un composé de formule (I) suivant la revendication 1, ou un ester de celui-ci acceptable du point de vue pharmaceutique, ou un sel de celui-ci acceptable du point de pharmaceutique, caractérisé en ce que le procédé comprend :
(A) la réaction d'un composé de formule générale (III)

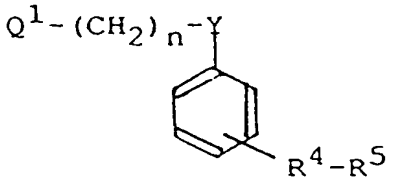
R^o-X-Q (III)

dans laquelle R^o et X sont tels que définis à propos de la formule (I) et Q représente un groupe de formule (a) ou (b) :



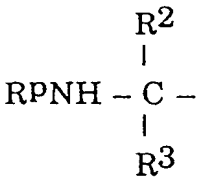
(a) (b)

dans laquelle R^{14} représente un groupe hydroxy ou un groupe hydroxy protégé et $X^{1'}$ est un groupe mobile,
avec un composé de formule générale (IV) :



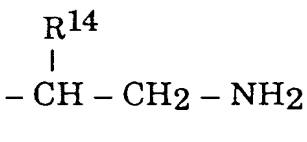
(IV)

dans laquelle R^4, R^5, n et Y sont tels que définis pour la formule (I), et
Q^1 représente un groupe de formule (F) :



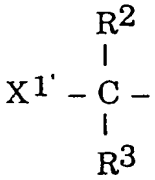
(F)

dans laquelle R^2 et R^3 sont tels que définis à propos de la formule (I), et R^p représente un atome d'hydrogène, un groupe protecteur, de préférence un groupe benzyle, ou la partie R^1 définie plus haut;
ou dans le composé mentionné plus haut de formule (III), Q représente un groupe de formule (c) :



(c)

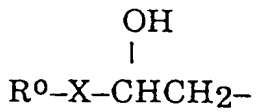
dans laquelle R^{14} est tel que défini plus haut,
et dans le composé mentionné plus haut de formule (IV), Q^1 représente un groupe de formule (g) :



(g)

dans laquelle R^2, R^3 et $X^{1'}$ sont tels que définis plus haut; ou

(B) pour des composés de formule (I) dans laquelle R^1 représente uniquement la partie :



telle qu'elle définie plus haut, le procédé comprend la réaction d'un composé de formule (I) dans laquelle R^1 représente un atome d'hydrogène, avec :

(i) un composé de formule (IIIA) :

R^o-X-Q (IIIA)

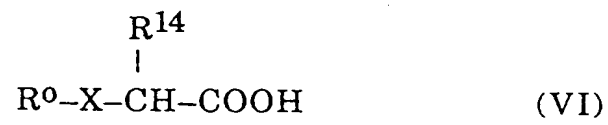
dans laquelle R^o et X sont tels définis pour la formule (I) et Q représente un groupe représenté par les formules (a) ou (b) telles que définies plus haut; ou

(ii) un composé de formule (V) :

R^o-X-CO-CHO (V)

dans laquelle R^o et X sont tels définis pour la formule (I);
et le traitement ultérieur avec un agent réducteur; ou

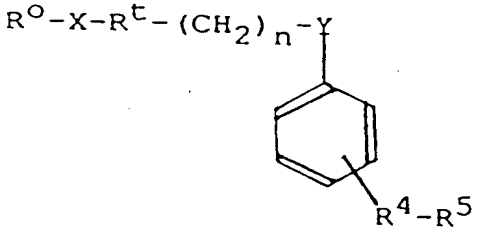
(iii) un composé de formule (VI) :



(VI)

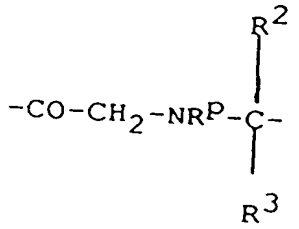
dans laquelle R^o et X sont tels définis pour la formule (I) et R^{14} représente un groupe hydroxy ou un groupe hydroxy protégé; ou

comprend la réduction d'un composé de formule générale (VII) :

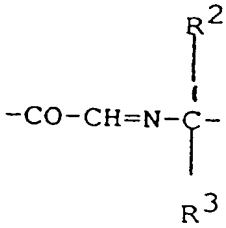


(VII)

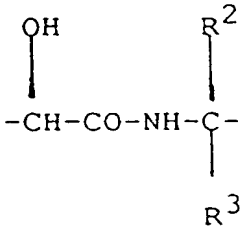
dans laquelle R^o, R^4, R^5, X, Y et n sont tels que définis pour la formule (I) et R^t représente un groupe de formule :



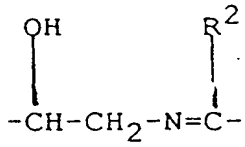
(i),



(ii),

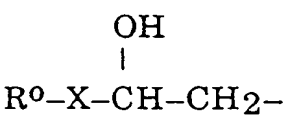


(iii),



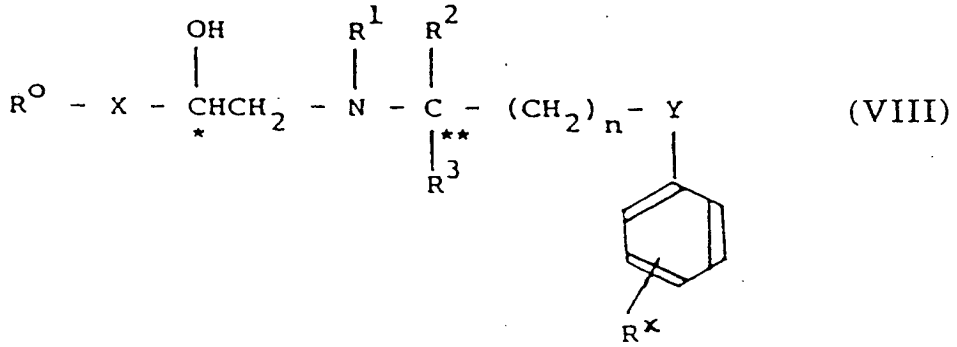
(iv)

dans lesquelles R^p est un atome d'hydrogène ou un groupe protecteur, de préférence un groupe benzyle, R^2 et R^3 sont tels que définis pour la formule (I);
et si cela est nécessaire, la conversion d'un composé de formule (I) dans laquelle R^1 représente un atome d'hydrogène en un composé de formule (I) dans laquelle R^1 représente une partie de formule :



dans laquelle R^o et X sont tels définis plus haut, par réaction du composé de formule (I), dans laquelle R^1 représente un atome d'hydrogène, avec un composé représenté par les formules (IIIA), (V) ou (VI) tels que définies plus haut; ou

(C) à partir d'un composé de formule (VIII) :



(VIII)

dans laquelle R^0, R^1, R^2, R^3, X, n et Y sont tels que définis pour la formule (I) et R^x représente une partie pouvant être convertie en une partie $-R^4-R^5-$;
et ensuite, si cela est nécessaire, la réalisation d'une ou de plusieurs des étapes suivantes :
(i) élimination d'un quelconque groupe protecteur;
(ii) conversion d'un composé de formule (I) en un autre composé de formule (I)
(iii) conversion d'un sel de formule (I) en un composé libre de formule (I);
(iv) préparation d'un ester acceptable du point de vue pharmaceutique d'un composé de formule (I);
(v) préparation d'un sel acceptable du point de vue pharmaceutique d'un composé de formule (I) ou d'un ester de celui-ci.

6. Composition pharmaceutique comprenant un composé de formule générale (I) telle que définie dans la revendication 1, ou un ester acceptable du point de vue pharmaceutique de celui-ci, ou un sel acceptable du point de vue pharmaceutique de celui-ci et un support acceptable du point de vue pharmaceutique pour celui-ci.

7. Composé de formule générale (I) telle que définie dans la revendication 1, ou ester acceptable du point de vue pharmaceutique de celui-ci, ou sel acceptable du point de vue pharmaceutique de celui-ci, utilisable en tant que substance thérapeutique active.

8. Composé de formule générale (I) telle que définie dans la revendication 1, ou ester acceptable du point de vue pharmaceutique de celui-ci, ou sel acceptable du point de vue pharmaceutique de celui-ci, utilisable dans le traitement de l'obésité et/ou de l'hyperglycémie chez l'homme ou des mammifères non humains.

9. Utilisation d'un composé de formule générale (I) ou d'un ester acceptable du point de vue pharmaceutique de celui-ci ou d'un sel acceptable du point de vue pharmaceutique de celui-ci, dans la fabrication d'un médicament pour le traitement de l'obésité ou de l'hyperglycémie.

10. Méthode pour améliorer la prise de poids et/ou améliorer le rendement de l'utilisation de la nourriture et/ou augmenter la masse de viande maigre des animaux sur pied, qui comprend l'administration à ces animaux sur pied, d'une quantité non toxique efficace d'un composé de formule générale (I) ou d'un ester acceptable du point de vue vétérinaire de celui-ci ou d'un sel acceptable du point de vue vétérinaire de celui-ci.